

STIC Search Report

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**TO: Ralph J Gitomer
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Art Unit: 1655
Monday, October 24, 2005**

Case Serial Number: 10/749714

**From: Noble Jarrell
Location: Biotech-Chem Library
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Search Notes

=> d his full

(FILE 'HOME' ENTERED AT 10:15:29 ON 24 OCT 2005)

FILE 'HCAPLUS' ENTERED AT 10:15:40 ON 24 OCT 2005

L1 1 SEA ABB=ON PLU=ON (US2004248231 OR US6713276 OR US2002159991)
/PN OR (US2003-749714# OR US2001-886143# OR US2000-215729#)/AP,
PRN

FILE 'REGISTRY' ENTERED AT 10:17:57 ON 24 OCT 2005

FILE 'HCAPLUS' ENTERED AT 10:17:57 ON 24 OCT 2005
L2 TRA L1 1- RN : 10 TERMS

FILE 'REGISTRY' ENTERED AT 10:17:58 ON 24 OCT 2005
L3 10 SEA ABB=ON PLU=ON L2

FILE 'WPIX' ENTERED AT 10:18:02 ON 24 OCT 2005

L4 1 SEA ABB=ON PLU=ON (US2004248231 OR US6713276 OR US2002159991)
/PN OR (US2003-749714# OR US2001-886143# OR US2000-215729#)/AP,
PRN

=> b hcap

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FILE COVERS 1907 - 24 Oct 2005 VOL 143 ISS 18

FILE LAST UPDATED: 23 Oct 2005 (20051023/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l1 tot

L1 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:10716 HCAPLUS

DN 136:81953

ED Entered STN: 04 Jan 2002

TI Non-amyloidogenic processing of β -amyloid precursor protein
(β APP) by β -secretase BACE2, use in suppression of
 β -amyloid production and screening of Alzheimer's disease drug
candidates

IN Cordell, Barbara; Schimmoller, Frauke; Liu, Yu-Wang; Quon, Diana Hom

PA Scios Inc., USA

SO PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12P021-00

CC 7-2 (Enzymes)

Section cross-reference(s): 9, 14

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002000913	A2	20020103	WO 2001-US20465	20010627 <--
	WO 2002000913	C2	20021024		
	WO 2002000913	A3	20030313		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, VZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 2002159991	A1	20021031	US 2001-886143	20010620 <--
	US 6713276	B2	20040330		
	CA 2413209	AA	20020103	CA 2001-2413209	20010627 <--
	EP 1315516	A2	20030604	EP 2001-948768	20010627 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
	JP 2004501652	T2	20040122	JP 2002-506227	20010627 <--
	US 2004248231	A1	20041209	US 2003-749714	20031231 <--
PRAI	US 2000-215729P	P	20000628	<--	
	US 2001-886143	A3	20010620	<--	
	WO 2001-US20465	W	20010627		

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
	WO 2002000913	ICM	C12P021-00
	WO 2002000913	ECLA	C07K014/47A3; C12N009/64F
	US 2002159991	NCL	424/094.630
		ECLA	C07K014/47A3; C12N009/64F
	JP 2004501652	FTERM	4B063/QA18; 4B063/QQ79; 4B063/QR16; 4B063/QR48; 4B063/QR56; 4B063/QS02; 4B063/QX07; 4B064/AG01; 4B064/CA21; 4B064/CB06; 4B064/CC03; 4B064/CD20; 4B064/DA01; 4B064/DA13; 4C084/AA19; 4C084/DC50; 4C084/NA14; 4C084/ZA02; 4C084/ZA16
	US 2004248231	NCL	435/023.000
		ECLA	C07K014/47A3; C12N009/64F

AB The present invention is based on the findings that BACE2, a homolog of β -secretase BACE, is able to stimulate processing of APP in a non-amyloidogenic pathway, thereby suppressing the level of A β . Accordingly, the present invention provides methods and means for the identification and use of modulators of this unique activity of BACE2 to suppress A β production. The compds. identified using the methods and means provided herein may be used as potential candidates for the treatment of Alzheimer's disease and other neurol. diseases. Exptl. data disclosed herein confirm that BACE2 indeed possesses β -secretase activity when reconstituting β -secretase cleavage in a cellfree assay using wildtype (wt) or Swedish mutant forms of APP751 as a substrate. However, this activity is weaker than the β -secretase activity of BACE. The invention is further based on the unexpected finding that while BACE2 overexpression in HEK293 cells had a moderate effect on β -NTF formation, it strikingly suppressed A β production in either the presence or absence of addnl. exogenous copies of BACE. BACE2 also modulated A β levels in neuronal SKN cells and thus its effect was not restricted to nonneuronal HEK293 cells. The suppression of A β production by BACE2 did not appear to require its ability to cleave at the β -secretase site. A levels were similarly suppressed in cells carrying a C-terminal 100-amino acids fragment of amyloid precursor protein (APP) truncated to mimic β -secretase cleavage. It is suggested that BACE2 functions as a modulator of A production by promoting the alternative non-amyloidogenic APP processing pathway such as that mediated by α -secretase activity. Taken together, these data indicate that

the ability of BACE2 to suppress A production reflects enhanced α -secretase-like activity that is independent of prior β -secretase cleavage. This α -secretase-like activity of BACE2 promotes the non-amyloidogenic processing of APP or APP fragments and reduces the production of A β . In summary, results disclosed herein indicate that BACE2 possesses weaker β -secretase activity than BACE and competes with BACE in an allosteric manner. This competition is further enhanced when mutating the critical aspartate of BACE2 thereby eliminating its β -secretase activity. We also demonstrated that BACE2 interferes with A β production by an enzymic mechanism that depends on its proteolytic activity. BACE2 appears critically involved in APP processing towards the non-amyloidogenic pathway by promoting an α -secretase-like cleavage which results in reduced A β generation.

ST nonamyloidogenic APP processing secretase BACE2 drug screening Alzheimer disease

IT Nervous system

(central, reducing A β deposit in; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT Alzheimer's disease

Drug screening

(non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT Amyloid precursor proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study) (non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT Brain

(reducing A β deposit in; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT Amyloid

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)

(β -; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT Amyloid precursor proteins

RL: ANT (Analyte); ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(β -CTF of, formation by BACE2 of; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT 148125-60-4, A4751 Amyloid protein precursor

RL: BSU (Biological study, unclassified); BIOL (Biological study) (cleavage by BACE2; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT 158736-49-3, Aspartic protease BACE2

RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); CAT (Catalyst use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)

IT 386303-49-7, 1: PN: WO0200913 SEQID: 1 unclaimed DNA 386303-51-1
386303-52-2
RL: PRP (Properties)
(unclaimed nucleotide sequence; non-amyloidogenic processing of
 β -amyloid precursor protein (β APP) by β -secretase BACE2,
use in suppression of β -amyloid production and screening of
Alzheimer's disease drug candidates)

IT 386303-50-0
RL: PRP (Properties)
(unclaimed protein sequence; non-amyloidogenic processing of
 β -amyloid precursor protein (β APP) by β -secretase BACE2,
use in suppression of β -amyloid production and screening of
Alzheimer's disease drug candidates)

IT 387398-33-6 387398-35-8
RL: PRP (Properties)
(unclaimed sequence; non-amyloidogenic processing of β -amyloid
precursor protein (β APP) by β -secretase BACE2, use in
suppression of β -amyloid production and screening of Alzheimer's
disease drug candidates)

IT 338454-52-7, γ -Secretase 338455-07-5, α -Secretase
RL: BUU (Biological use, unclassified); CAT (Catalyst use); BIOL
(Biological study); USES (Uses)
(use in inhibiting A β formation; non-amyloidogenic processing of
 β -amyloid precursor protein (β APP) by β -secretase BACE2,
use in suppression of β -amyloid production and screening of
Alzheimer's disease drug candidates)

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FILE 'REGISTRY' ENTERED AT 10:18:56 ON 24 OCT 2005

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STRUCTURE FILE UPDATES: 23 OCT 2005 HIGHEST RN 865836-54-0

DICTIONARY FILE UPDATES: 23 OCT 2005 HIGHEST RN 865836-54-0

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* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

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for details.

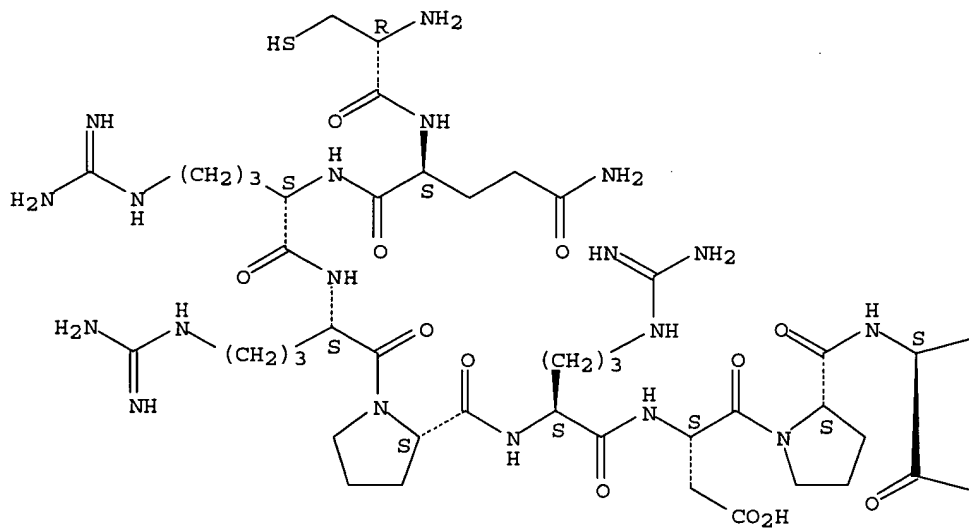
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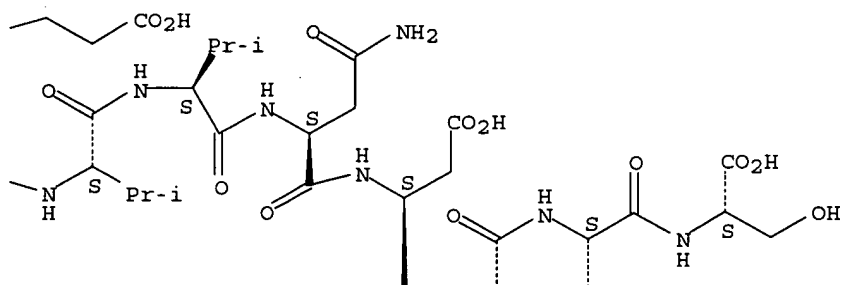
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asparaginyl-L- α -aspartyl-L- α -glutamyl-L-seryl- (9CI) (CA
INDEX NAME)
OTHER NAMES:
CN 6: PN: WO0200913 SEQID: 6 unclaimed sequence
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SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.

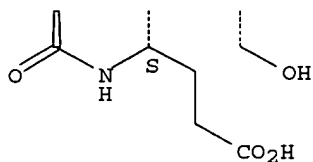
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PAGE 2-B



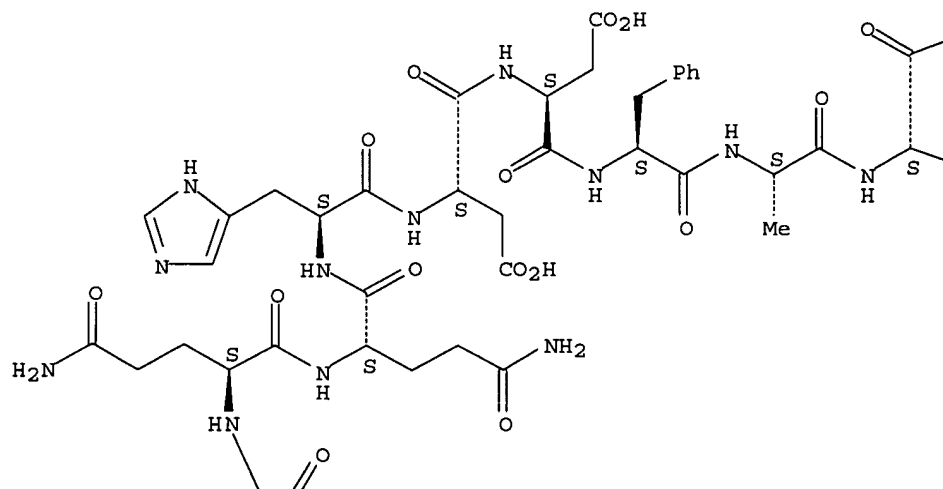
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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

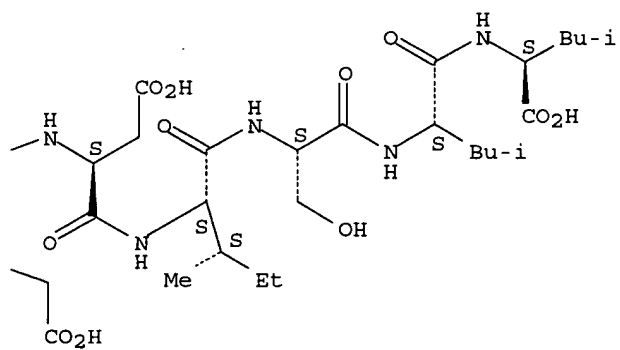
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ED Entered STN: 28 Jan 2002
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SR CA
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Absolute stereochemistry.

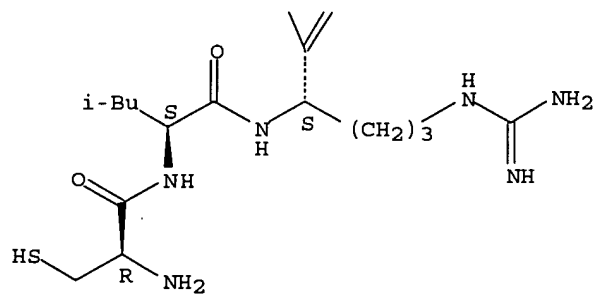
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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 3 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 386303-52-2 REGISTRY
ED Entered STN: 24 Jan 2002
CN DNA, d(C-A-A-A-G-T-T-A-C-T-G-C-T-T-C-C-A-G-T-G-G-C-A-A-C-G-A-G-A-A-T-C-T-G-T-A-G-C) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4: PN: WO0200913 SEQID: 4 unclaimed DNA
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

***RELATED SEQUENCES AVAILABLE WITH SEQLINK**

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*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 4 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 386303-51-1 REGISTRY
ED Entered STN: 24 Jan 2002
CN DNA, d(G-C-T-A-C-A-G-A-T-T-C-T-C-G-T-T-G-C-C-A-C-T-G-G-A-A-G-C-A-G-T-A-A-C-T-T-T-G) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: WO0200913 SEQID: 3 unclaimed DNA
FS NUCLEIC ACID SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 5 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 386303-50-0 REGISTRY
ED Entered STN: 24 Jan 2002
CN 2: PN: WO0200913 SEQID: 2 unclaimed protein (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

***RELATED SEQUENCES AVAILABLE WITH SEQLINK**

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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 6 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 386303-49-7 REGISTRY
ED Entered STN: 24 Jan 2002
CN 1: PN: WO0200913 SEQID: 1 unclaimed DNA (9CI) (CA INDEX NAME)
FS NUCLEIC ACID SEQUENCE
MF Unspecified

CI MAN
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

****RELATED SEQUENCES AVAILABLE WITH SEQLINK****

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1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 7 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 338455-07-5 REGISTRY
ED Entered STN: 25 May 2001
CN α -Secretase (9CI) (CA INDEX NAME)
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

***** STRUCTURE DIAGRAM IS NOT AVAILABLE *****

139 REFERENCES IN FILE CA (1907 TO DATE)

139 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 8 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 338454-52-7 REGISTRY
ED Entered STN: 25 May 2001
CN γ -Secretase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ϵ -Secretase
MF Unspecified
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SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

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4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

715 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 9 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 158736-49-3 REGISTRY
ED Entered STN: 04 Nov 1994
CN β -Secretase (9CI) (CA INDEX NAME)
OTHER NAMES:
CN β Protein amyloidogenase
CN β -Amyloid converting enzyme
CN β -Amyloid protein precursor secretase
CN β -Site APP-cleaving enzyme
CN β -site APP-cleaving enzyme 1
CN Amyloid precursor protein secretase
CN APP secretase
CN Aspartic protease BACE
CN Aspartic protease BACE1
CN Aspartic proteinase BACE1
CN D-Aspartyl- β -amyloid secretase
CN Memapsin 2
CN Protease Asp2
CN Proteinase Asp2
CN Proteinase BACE1
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN, CIN, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
974 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 10 OF 10 REGISTRY COPYRIGHT 2005 ACS on STN
RN 148125-60-4 REGISTRY
ED Entered STN: 16 Jun 1993
CN Proteinase inhibitor, protease-nexin II (9CI) (CA INDEX NAME)
OTHER NAMES:
CN A4751 amyloid protein precursor
CN Amyloid A4751 glycoproteins
CN Amyloid A4751 proteins
CN Glycoproteins, amyloid A4751
CN Glycoproteins, amyloid A4751
CN Plasminogen activator inhibitor PN 2
CN Protease-nexin 2
CN Protease-nexin II
CN Proteins, ABPP 751
CN Proteins, amyloid A4751
CN Proteins, amyloid precursor protein 751
CN Proteins, APP751
CN Proteins, BPP751
CN Proteins, protease-nexins, II
CN Proteins, proteinase-nexins II
MF Unspecified
CI MAN
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, PROMT, TOXCENTER, USPAT2, USPATFULL

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131 REFERENCES IN FILE CA (1907 TO DATE)
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131 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> b wpix;d all 14 tot
FILE 'WPIX' ENTERED AT 10:19:08 ON 24 OCT 2005
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FILE LAST UPDATED: 19 OCT 2005 <20051019/UP>
MOST RECENT DERWENT UPDATE: 200567 <200567/DW>
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FOR DETAILS. <<<

'BIX BI,ABEX' IS DEFAULT SEARCH FIELD FOR 'WPIX' FILE

L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 AN 2002-139929 [18] WPIX
 DNC C2002-043150
 TI Modulating enzymatic production of beta amyloid peptide from its precursor protein (APP) for treating Alzheimer's disease, comprises contacting APP with a beta site APP-cleaving enzyme 2 polypeptide, its agonist or antagonist.
 DC B04 D16
 IN CORDELL, B; LIU, Y; QUON, D H; SCHIMMOLLER, F; SCHIMMOELLER, F
 PA (SCIO-N) SCIOS INC; (CORD-I) CORDELL B; (LIUY-I) LIU Y; (QUON-I) QUON D H; (SCHI-I) SCHIMMOLLER F
 CYC 95
 PI WO 2002000913 A2 20020103 (200218)* EN 48 C12P021-00
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 NL OA PT SD SE SL SZ TR TZ UG ZW
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 DZ EE ES FI GB GD GE GH GR HU ID IL IN IS JP KE KG KP KR KZ LC
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
 SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
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 US 2002159991 A1 20021031 (200274) A61K038-48 <--
 EP 1315516 A2 20030604 (200337) EN A61K038-48
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 US 6713276 B2 20040330 (200423) C12Q001-37 <--
 US 2004248231 A1 20041209 (200481) C12Q001-37 <--
 ADT WO 2002000913 A2 WO 2001-US20465 20010627; AU 2001070204 A AU 2001-70204 20010627; US 2002159991 A1 Provisional US 2000-215729P 20000628, US 2001-886143 20010620; EP 1315516 A2 EP 2001-948768 20010627, WO 2001-US20465 20010627; JP 2004501652 W WO 2001-US20465 20010627, JP 2002-506227 20010627; US 6713276 B2 Provisional US 2000-215729P 20000628, US 2001-886143 20010620; US 2004248231 A1 Provisional US 2000-215729P 20000628, Div ex US 2001-886143 20010620, US 2003-749714 20031231
 FDT AU 2001070204 A Based on WO 2002000913; EP 1315516 A2 Based on WO 2002000913; JP 2004501652 W Based on WO 2002000913; US 2004248231 A1 Div ex US 6713276
 PRAI US 2000-215729P 20000628; US 2001-886143 20010620; US 2003-749714 20031231
 IC ICM A61K038-48; C12P021-00; C12P021-06; C12Q001-37
 ICS A61K038-00; A61K045-00; A61P025-00; A61P025-28; C12N009-99; G01N033-50
 AB WO 200200913 A UPAB: 20020319
 NOVELTY - Modulating (M1) the enzymatic production of beta -amyloid peptide (A beta) from beta -amyloid precursor protein (APP) or its fragment, involves contacting the APP or its fragment with a beta -site APP-cleaving enzyme (BACE)-2 polypeptide, its agonist or antagonist.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
 (1) inhibiting (M2) the release of a full-length A beta polypeptide from APP or its fragment, by cleaving APP or its fragment by a BACE2 polypeptide or its agonist at a site interfering with beta -secretase processing of the APP or its fragment;
 (2) identifying (M3) a modulator of the enzymatic production of A beta from APP or its fragment, by contacting APP or its fragment and BACE2 with a candidate compound (CC) and monitoring the effect of CC on the production of A beta ; and
 (3) a modulator (I) of the enzymatic production of A beta from APP or its fragment, identified by (M3).
 ACTIVITY - Neuroprotective; nootropic.

MECHANISM OF ACTION - Enzymatic production inhibitor; release of A beta inhibitor; BACE2 agonist (claimed). Variable amounts of BACE2 or BACE expression plasmids were co-transfected with a constant amount of DNA encoding APP751sw (Swedish double mutant) substrate cDNA. Cell supernatants were collected 48 hours or 72 hours post-transfection and analyzed for alpha -NTF (undefined), -NTF, total A and A 42. Expression of APP751sw alone led to a significant increase in -NTF, alpha -NTF, total and A 42 compared to mock-transfected cells. This suggested that endogenous secretases were not limiting for -NTF or A formation under these conditions. When BACE was expressed in addition to APP751sw, -NTF levels were further increased, and alpha -NTF levels were proportionally reduced. Under these conditions, A production was not significantly stimulated. When co-transfecting BACE2 with APP751sw, the effect on -NTF levels was very similar to that of BACE suggesting that BACE had some secretase activity in vivo. In fact, the levels of alpha -NTF and -NTF generated by BACE2 and BACE were inversely proportional to each other and added up to basically the same total optical density (OD) values as in cells transfected with APP751sw alone (total OD approximately 2.59 for APP751sw alone, approximately 2.5 with BACE2, and approximately 2.3 with BACE). The combined values of alpha -NTF and -NTF for BACE was slightly lower since the -NTF assay had reached saturation. The different ratios of alpha -NTF and -NTF values under the different transfection conditions were consistent with the competition of secretase and secretase for the same substrate. The slightly higher levels of -NTF in conditioned medium from BACE2 versus BACE transfected cells reflects in part the fact that BACE2 is the weaker secretase. In contrast to BACE, BACE2 expression resulted in the striking reduction of total A and A 42 to levels found in mock-transfected cells. Thus, BACE2 suppressed A production without significantly affecting the formation of either alpha -NTF and -NTF.

USE - (I) and BACE2 are useful for reducing the amount of beta -amyloid deposits in the central nervous system (CNS) (e.g. brain) of a mammal, by the administration of BACE2 or its agonist to the mammal, e.g. a human. BACE2 and (I) are useful for the treatment or the prevention of Alzheimer's disease (AD), an AD-type pathology or cerebral amyloid angiopathy in a mammalian patient e.g. human, at a risk of developing AD, AD-type pathology or cerebral amyloid angiopathy (claimed).

Dwg.0/8

FS CPI
FA AB; DCN
MC CPI: B04-L01; B04-M01; B04-N02; B11-C08E3; B12-K04E; B14-J01A4; B14-L01;
B14-L06; B14-N16; D05-C03; D05-C11; D05-H09

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=> d his

(FILE 'HOME' ENTERED AT 10:15:29 ON 24 OCT 2005)

FILE 'HCAPLUS' ENTERED AT 10:15:40 ON 24 OCT 2005

L1 1 (US2004248231 OR US6713276 OR US2002159991)/PN OR (US2003-74971

FILE 'REGISTRY' ENTERED AT 10:17:57 ON 24 OCT 2005

FILE 'HCAPLUS' ENTERED AT 10:17:57 ON 24 OCT 2005

L2 TRA L1 1- RN : 10 TERMS

FILE 'REGISTRY' ENTERED AT 10:17:58 ON 24 OCT 2005

L3 10 SEA L2

FILE 'WPIX' ENTERED AT 10:18:02 ON 24 OCT 2005

L4 1 L1

FILE 'REGISTRY' ENTERED AT 10:27:18 ON 24 OCT 2005

L5 24 (BACE2 OR BACE (W) 2 OR (BAPP? OR BETA(W) (APP OR AMYLOID P

L6 151 (BSECRETASE? OR B(W)SECRETAS?)/CNS

L7 167 L5-6

L8 6 (MEMAPSIN2 OR MEMAPSIN (W)2)/CNS

L9 171 L7,L8

FILE 'HCAPLUS' ENTERED AT 10:33:14 ON 24 OCT 2005

L10 1030 L9

L11 58 MEMAPSIN2 OR MEMAPSIN(W)2

L12 937 BSECRETASE? OR B(W)SECRETAS?

L13 3085 BACE2 OR BACE (W) 2 OR (BAPP? OR BETA(W) (APP OR AMYLOID PR
E ALZHEIMER/CT

E E9+ALL

L14 QUE "ALZHEIMER'S DISEASE"+OLD,NT/CT

E E26+ALL

L15 79174 AGING, ANIMAL+OLD,NT/CT

E AMYLOID PRECURSOR PROTEINS/CT

E E3+ALL

L16 4880 AMYLOID PRECURSOR PROTEINS+OLD,NT/CT

E AMYLOIDOSIS/CT

E E3+ALL

L17 3539 AMYLOIDOSIS+OLD,NT/CT

E "ANTI-ALZHEIMER'S AGENTS"/CT

E E3+ALL

L18 6449 "ANTI-ALZHEIMER'S AGENTS"/CT

E COGNITION ENHANCERS/CT

E E3+ALL

L19 3595 COGNITION ENHANCERS+OLD/CT

E AMYLOID/CT

E E3+ALL

L20 93386 AMYLOID+OLD,NT/CT

E NEUROFIBRILLARY TANGLE/CT

E E3+ALL

L21 1268 NEUROFIBRILLARY TANGLE+OLD/CT

E PRESENILINS/CT

E E3+ALL

L22 1643 PRESENILINS/CT

E TAU FACTOR/CT

E E3+ALL

L23 3324 TAU FACTOR+OLD/CT

E B-SECRETASE/CT

E E3+ALL

L24 974 B-SECRETASE/CT

L25 1609 L10,L11,L12,L13,L24 AND L14-23

E CORDELL B/AU

L26 111 E3-6

E SCHIMMOLLER F/AU

L27 8 E4
E LIU Y/AU
L28 1988 E3,E37-39
E LIU YU/AU
L29 1145 E3
E LIU YU W/AU
L30 9 E4
E LIU YUW/AU
L31 11 E4
E QUON D/AU
L32 72 E3-5,E9-11
L33 221 SCIOS/CS,PA
L34 21 L25 AND L26-33
L35 35605 DRUG SCREENING+OLD/CT
L36 1588 L25 NOT L34
L37 99 L36 AND L35
L38 QUE PY<=2000 OR AY<=2000 OR PRY<=2000 OR PD<20000628 OR AD<=200
L39 50 L37 AND L38
L40 50 L39 AND (BIOL+NT OR ANST+NT)/RL
SEL AN 21 23 26-28 37 38 43 44 L40
L41 9 E1-18 AND L40
SEL AN 2 7-8 10 11 16 L40
L42 6 E19-30 AND L40
L43 15 L41,L42

=> b hcap

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L34 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:865010 HCAPLUS
DN 138:361960
ED Entered STN: 14 Nov 2002
TI Amyloid forming proteases: therapeutic targets for Alzheimer's disease
AU Schimmoller, Frauke; Higaki, Jeffrey N.; Cordell, Barbara
CS Scios Inc., Sunnyvale, CA, 94085, USA
SO Current Pharmaceutical Design (2002), 8(28), 2521-2531
CODEN: CPDEFP; ISSN: 1381-6128
PB Bentham Science Publishers
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)

AB A review. Alzheimer's disease is an age-related neurodegenerative disease which causes global loss of cognitive function. Drug treatment for Alzheimer's disease has been limited to agents that ameliorate behavioral symptoms but these agents are without effect on disease progression. Rational drug design for the treatment of Alzheimer's disease now seems possible. As a result of major advances in medical research in this area, knowledge of the etiol. of Alzheimer's disease is rapidly being understood. This information has uncovered relevant and novel targets for treatment. At the center of the etiol. progression of this disease is β -amyloid. A substantial body of evidence strongly suggests that this small protein is critical to the development of Alzheimer's disease. The β -amyloid protein is generated by two different proteolytic cleavages. Recently, the proteases responsible for producing the β -amyloid protein have been identified. The proteases represent viable targets for therapeutic intervention against Alzheimer's disease. In this review, we describe the biol. characteristics of the β -amyloid-forming proteases in the context of pharmaceutical development.

ST review amyloid protease drug target Alzheimer disease

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(BACE; amyloid forming proteases as drug targets for Alzheimer's disease)

IT Alzheimer's disease

Anti-Alzheimer's agents

(amyloid forming proteases as drug targets for Alzheimer's disease)

IT Nervous system, disease

(degeneration; amyloid forming proteases as drug targets for Alzheimer's disease)

IT Amyloid

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(β -; amyloid forming proteases as drug targets for Alzheimer's disease)

IT 158736-49-3, β -Secretase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(amyloid forming proteases as drug targets for Alzheimer's disease)

RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L34 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:10716 HCAPLUS

DN 136:81953

ED Entered STN: 04 Jan 2002

TI Non-amyloidogenic processing of β -amyloid precursor protein (.
beta.APP) by β -secretaseBACE2, use in suppression of β -amyloid production and
screening of Alzheimer's disease drug candidates

IN Cordell, Barbara; Schimmoller, Frauke; Liu,

Yu-Wang; Quon, Diana Hom

PA Scios Inc., USA

SO PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12P021-00

CC 7-2 (Enzymes)

Section cross-reference(s): 9, 14

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002000913	A2	20020103	WO 2001-US20465	20010627
	WO 2002000913	C2	20021024		
	WO 2002000913	A3	20030313		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	US 2002159991	A1	20021031	US 2001-886143	20010620
	US 6713276	B2	20040330		
	CA 2413209	AA	20020103	CA 2001-2413209	20010627
	EP 1315516	A2	20030604	EP 2001-948768	20010627
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
	JP 2004501652	T2	20040122	JP 2002-506227	20010627
	US 2004248231	A1	20041209	US 2003-749714	20031231
PRAI	US 2000-215729P	P	20000628		
	US 2001-886143	A3	20010620		
	WO 2001-US20465	W	20010627		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002000913	ICM	C12P021-00
WO 2002000913	ECLA	C07K014/47A3; C12N009/64F
US 2002159991	NCL	424/094.630
	ECLA	C07K014/47A3; C12N009/64F
JP 2004501652	FTERM	4B063/QA18; 4B063/QQ79; 4B063/QR16; 4B063/QR48; 4B063/QR56; 4B063/QS02; 4B063/QX07; 4B064/AG01; 4B064/CA21; 4B064/CB06; 4B064/CC03; 4B064/CD20; 4B064/DA01; 4B064/DA13; 4C084/AA19; 4C084/DC50; 4C084/NA14; 4C084/ZA02; 4C084/ZA16
US 2004248231	NCL	435/023.000
	ECLA	C07K014/47A3; C12N009/64F

AB The present invention is based on the findings that BACE2, a homolog of β -secretase BACE, is able to stimulate processing of APP in a non-amyloidogenic pathway, thereby suppressing the level of A β . Accordingly, the present invention provides methods and means for the identification and use of modulators of this unique activity

of BACE2 to suppress A β production. The compds. identified using the methods and means provided herein may be used as potential candidates for the treatment of Alzheimer's disease and other neurol. diseases. Exptl. data disclosed herein confirm that BACE2 indeed possesses β -secretase activity when reconstituting β -secretase cleavage in a cellfree assay using wildtype (wt) or Swedish mutant forms of APP751 as a substrate. However, this activity is weaker than the β -secretase activity of BACE. The invention is further based on the unexpected finding that while BACE2 overexpression in HEK293 cells had a moderate effect on β -NTF formation, it strikingly suppressed A β production in either the presence or absence of addnl. exogenous copies of BACE. BACE2 also modulated A β levels in neuronal SKN cells and thus its effect was not restricted to nonneuronal HEK293 cells. The suppression of A β production by BACE2 did not appear to require its ability to cleave at the .beta.-secretase site. A levels were similarly suppressed in cells carrying a C-terminal 100-amino acids fragment of amyloid precursor protein (APP) truncated to mimic β -secretase cleavage. It is suggested that BACE2 functions as a modulator of A production by promoting the alternative non-amyloidogenic APP processing pathway such as that mediated by α -secretase activity. Taken together, these data indicate that the ability of BACE2 to suppress A production reflects enhanced α -secretase-like activity that is independent of prior .beta.-secretase cleavage. This α -secretase-like activity of BACE2 promotes the non-amyloidogenic processing of APP or APP fragments and reduces the production of A β . In summary, results disclosed herein indicate that BACE2 possesses weaker .beta.-secretase activity than BACE and competes with BACE in an allosteric manner. This competition is further enhanced when mutating the critical aspartate of BACE2 thereby eliminating its .beta.-secretase activity. We also demonstrated that BACE2 interferes with A β production by an enzymic mechanism that depends on its proteolytic activity. BACE2 appears critically involved in APP processing towards the non-amyloidogenic pathway by promoting an α -secretase-like cleavage which results in reduced AP3 generation.

- ST nonamyloidogenic APP processing secretase BACE2 drug screening
Alzheimer disease
- IT Nervous system
(central, reducing A β deposit in; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)
- IT Alzheimer's disease
Drug screening
(non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)
- IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)
- IT Brain
(reducing A β deposit in; non-amyloidogenic processing of β -amyloid precursor protein (β APP) by β -secretase BACE2, use in suppression of β -amyloid production and screening of Alzheimer's disease drug candidates)
- IT Amyloid
RL: ADV (Adverse effect, including toxicity); BSU (Biological study,

unclassified); BIOL (Biological study)
 (β-; non-amyloidogenic processing of β-amyloid precursor
 protein (β APP) by β -
secretase BACE2, use in suppression of β-amyloid
 production and screening of Alzheimer's disease drug candidates)

IT **Amyloid precursor proteins**

RL: ANT (Analyte); ARU (Analytical role, unclassified); BUU (Biological
 use, unclassified); ANST (Analytical study); BIOL (Biological study); USES
 (Uses)

(β-CTF of, formation by **BACE2** of; non-amyloidogenic
 processing of β-amyloid precursor protein (β
 APP) by β -**secretase BACE2**,
 use in suppression of β-amyloid production and screening of
 Alzheimer's disease drug candidates)

IT 148125-60-4, A4751 Amyloid protein precursor

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (cleavage by **BACE2**; non-amyloidogenic processing of
 β-amyloid precursor protein (β APP) by
 β -**secretase BACE2**, use in suppression
 of β-amyloid production and screening of Alzheimer's disease drug
 candidates)

IT 158736-49-3, Aspartic protease **BACE2**

RL: ARU (Analytical role, unclassified); BSU (Biological study,
 unclassified); CAT (Catalyst use); ANST (Analytical study); BIOL
 (Biological study); USES (Uses)
 (non-amyloidogenic processing of β-amyloid precursor protein (β
 APP) by β -**secretase**
BACE2, use in suppression of β-amyloid production and
 screening of Alzheimer's disease drug candidates)

IT 386303-49-7, 1: PN: WO0200913 SEQID: 1 unclaimed DNA 386303-51-1
 386303-52-2

RL: PRP (Properties)
 (unclaimed nucleotide sequence; non-amyloidogenic processing of
 β-amyloid precursor protein (β APP) by
 β -**secretase BACE2**, use in suppression
 of β-amyloid production and screening of Alzheimer's disease drug
 candidates)

IT 386303-50-0

RL: PRP (Properties)
 (unclaimed protein sequence; non-amyloidogenic processing of
 β-amyloid precursor protein (β APP) by
 β -**secretase BACE2**, use in suppression
 of β-amyloid production and screening of Alzheimer's disease drug
 candidates)

IT 387398-33-6 387398-35-8

RL: PRP (Properties)
 (unclaimed sequence; non-amyloidogenic processing of β-amyloid
 precursor protein (β APP) by β -
secretase BACE2, use in suppression of β-amyloid
 production and screening of Alzheimer's disease drug candidates)

IT 338454-52-7, γ-Secretase 338455-07-5, α-Secretase

RL: BUU (Biological use, unclassified); CAT (Catalyst use); BIOL
 (Biological study); USES (Uses)
 (use in inhibiting Aβ formation; non-amyloidogenic processing of
 β-amyloid precursor protein (β APP) by
 β -**secretase BACE2**, use in suppression
 of β-amyloid production and screening of Alzheimer's disease drug
 candidates)

L34 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:914735 HCAPLUS

DN 136:165334

ED Entered STN: 19 Dec 2001

TI Specific spatial learning deficits become severe with age in
 β-amyloid precursor protein transgenic mice that harbor diffuse
 β-amyloid deposits but do not form plaques

AU Koistinaho, Milla; Ort, Michael; Cimadevilla, Jose M.; Vondrous, Roman;
 Cordell, Barbara; Koistinaho, Jari; Bures, Jan; Higgins, Linda S.
 CS Institute of Physiology, Academy of Sciences of the Czech Republic,
 Prague, 14220/4, Czech Rep.
 SO Proceedings of the National Academy of Sciences of the United States of
 America (2001), 98(25), 14675-14680
 CODEN: PNASA6; ISSN: 0027-8424
 PB National Academy of Sciences
 DT Journal
 LA English
 CC 14-10 (Mammalian Pathological Biochemistry)
 AB Memory impairment progressing to dementia is the main clin. symptom of
 Alzheimer's disease (AD). AD is characterized histol. by the presence of
 β -amyloid ($A\beta$) plaques and neurofibrillary tangles in specific
 brain regions. Although $A\beta$ derived from the $A\beta$ precursor
 protein (β -APP) is believed to play a central
 etiol. role in AD, it is not clear whether soluble and/or fibrillar forms are
 responsible for the memory deficit. We have generated and previously
 described mice expressing human wild-type β -APP751
 isoform in neurons. These transgenic mice recapitulate early histopathol.
 features of AD and form $A\beta$ deposits but no plaques. Here we describe
 a specific and progressive learning and memory impairment in these
 animals. In the Morris water maze, a spatial memory task sensitive to
 hippocampal damage, one pedigree already showed significant differences in
 acquisition in 3-mo-old mice that increased in severity with age and were
 expressed clearly in 6-mo- and 2-yr-old animals. The second transgenic
 pedigree displayed a milder impairment with a later age of onset.
 Performance deficits significantly decreased during the 6 days of training
 in young but not in aged transgenic animals. Both pedigrees of the
 transgenic mice differed from wild-type mice by less expressed increase of
 escape latencies after the platform position had been changed in the
 reversal experiment and by failure to prefer the goal quadrant in probe trials.
 Both pedigrees performed at wild-type level in a number of other tests (open
 field exploration and passive and active place avoidance). The results
 suggest that plaque formation is not a necessary condition for the
 neuronal β -APP751 transgene-induced memory
 impairment, which may be caused by β -APP
 overexpression, isoform misexpression, or elevated soluble $A\beta$.
 ST beta amyloid precursor protein spatial learning deficit transgenic mouse
 IT Mental disorder
 (memory retention defect; spatial learning deficits become severe with
 age in β -amyloid precursor protein transgenic mice that harbor
 diffuse β -amyloid deposits but do not form plaques)
 IT Memory, biological
 (retention defect; spatial learning deficits become severe with age in
 β -amyloid precursor protein transgenic mice that harbor diffuse
 β -amyloid deposits but do not form plaques)
 IT Aging, animal
 Alzheimer's disease
 Disease models
 Human
 Mus
 (spatial learning deficits become severe with age in β -amyloid
 precursor protein transgenic mice that harbor diffuse β -amyloid
 deposits but do not form plaques)
 IT Amyloid precursor proteins
 RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); BIOL (Biological study)
 (spatial learning deficits become severe with age in β -amyloid
 precursor protein transgenic mice that harbor diffuse β -amyloid
 deposits but do not form plaques)
 IT Learning
 (spatial, disorder; spatial learning deficits become severe with age in
 β -amyloid precursor protein transgenic mice that harbor diffuse
 β -amyloid deposits but do not form plaques)
 IT Gene, animal

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)

(β -APP751; spatial learning deficits become severe with age in β -amyloid precursor protein transgenic mice that harbor diffuse β -amyloid deposits but do not form plaques)

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L34 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:824049 HCAPLUS
DN 133:346509
ED Entered STN: 24 Nov 2000

TI β -Secretase from human brain and HEK-293 cells
and its use for screening drug modulators of β -
secretase activity

IN Zhong, Ziyang; Cordell, Barbara; Quon, Diana Hom;
Liu, Yu-Wang; Xu, Qiang

PA Scios Inc., USA; Eli Lilly and Company

SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2

DT Patent

LA English

IC A01N037-18; A01N043-04; A61K031-70; A61K038-00; C12N009-48; C12N009-64;
C12Q001-37; G01N033-53; G01N033-537; G01N033-543

CC 7-2 (Enzymes)
Section cross-reference(s): 63

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069262	A1	20001123	WO 2000-US13074	20000511
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2368624	AA	20001123	CA 2000-2368624	20000511
EP 1176871	A1	20020206	EP 2000-932358	20000511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002543815	T2	20021224	JP 2000-617730	20000511
US 2004132159	A1	20040708	US 2003-740865	20031218
PRAI US 1999-134074P	P	19990513		
US 2000-566746	A	20000509		
WO 2000-US13074	W	20000511		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000069262	IC	A01N037-18IC A01N043-04IC A61K031-70IC A61K038-00IC C12N009-48IC C12N009-64IC C12Q001-37IC G01N033-53IC G01N033-537IC G01N033-543
WO 2000069262	ECLA	C12N009/64F2C23; C12Q001/37
US 2004132159	NCL	435/226.000
	ECLA	C12N009/64F2C23; C12Q001/37

AB The invention concerns a novel β -secretase, a method of partially purifying this novel β -secretase, and its use in assays to screen for potential drug candidates against Alzheimer's disease and other neurol. diseases. The novel β -secretase has an estimated mol. weight of about 32-39 kDa or 22-26 kDa in HEK293 cell membrane exts. and human brain samples, resp., as calculated from radiation inactivation anal., and has a pH optimum at about pH 6.5-7.0.

ST secretase human characterization drug screening

IT Animal cell line

(Hek 293; β -secretase from human brain and HEK-293 cells and its use for screening drug modulators of β -secretase activity)

IT Cardiopolipins

Phosphatidylinositols

Phosphatidylserines

Phospholipids, biological studies

RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)

(stabilizer treatment prior to screening assays; β -
secretase from human brain and HEK-293 cells and its use for
screening drug modulators of β -secretase
activity)

IT Brain

Drug screening

(β -secretase from human brain and HEK-293
cells and its use for screening drug modulators of β -
secretase activity)

IT Amyloid precursor proteins

RL: ARG (Analytical reagent use); BPR (Biological process); BSU
(Biological study, unclassified); ANST (Analytical study); BIOL
(Biological study); PROC (Process); USES (Uses)

(β -secretase from human brain and HEK-293
cells and its use for screening drug modulators of β -
secretase activity)

IT Antibodies

RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical
study); BIOL (Biological study); USES (Uses)

(β -secretase from human brain and HEK-293
cells and its use for screening drug modulators of β -
secretase activity)

IT 158736-49-3P, β -Secretase

RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); PRP (Properties); PUR (Purification or recovery);
THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

(β -secretase from human brain and HEK-293
cells and its use for screening drug modulators of β -
secretase activity)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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- (2) Chrysler; US 5744346 A 1998 HCAPLUS
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L34 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:811590 HCAPLUS

DN 134:95421

ED Entered STN: 20 Nov 2000

TI Presenilin-1 and -2 are molecular targets for γ -secretase inhibitors

AU Seiffert, Dietmar; Bradley, Jodi D.; Rominger, Cynthia M.; Rominger, David
H.; Yang, Fude; Meredith, Jere E., Jr.; Wang, Qian; Roach, Arthur H.;
Thompson, Lorin A.; Spitz, Susan M.; Higaki, Jeffrey N.; Prakash, Shimoga
R.; Combs, Andrew P.; Copeland, Robert A.; Arneric, Stephen P.; Hartig,
Paul R.; Robertson, David W.; Cordell, Barbara; Stern, Andrew
M.; Olson, Richard E.; Zaczek, Robert

CS DuPont Pharmaceuticals Company, Wilmington, DE, 19880, USA

SO Journal of Biological Chemistry (2000), 275(44), 34086-34091

CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 1-11 (Pharmacology)

Section cross-reference(s): 7

AB Presenilins are integral membrane protein involved in the production of
amyloid β -protein. Mutations of the presenilin-1 and -2 gene are
associated with familial Alzheimer's disease and are thought to alter
 γ -secretase cleavage of the β -amyloid precursor protein,
leading to increased production of longer and more amyloidogenic forms of
 $A\beta$, the 4-kDa β -peptide. Here, we show that radiolabeled
 γ -secretase inhibitors bind to mammalian cell membranes, and a
benzophenone analog specifically photocross-links three major membrane
polypeptides. A pos. correlation is observed among these compds. for
inhibition of cellular $A\beta$ formation, inhibition of membrane binding
and crosslinking. Immunol. techniques establish N- and C-terminal

fragments of presenilin-1 as specifically cross-linked polypeptides. Furthermore, binding of γ -secretase inhibitors to embryonic membranes derived from presenilin-1 knockout embryos is reduced in a gene dose-dependent manner. In addition, C-terminal fragments of presenilin-2 are specifically cross-linked. Taken together, these results indicate that potent and selective γ -secretase inhibitors block A β formation by binding to presenilin-1 and -2.

ST secretase inhibitor membrane presenilin crosslinking

IT **Presenilins**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(1 and 2; presenilin-1 and -2 as mol. targets for γ -secretase inhibitors)

IT Cell membrane

Crosslinking

(presenilin-1 and -2 as mol. targets for γ -secretase inhibitors:
cell membrane binding)

IT 158736-49-3, γ -Secretase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(presenilin-1 and -2 as mol. targets for γ -secretase inhibitors)

IT 209986-17-4P 258864-62-9P 258864-67-4P 258864-68-5P 258864-80-1P
258870-13-2P 280568-31-2P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(presenilin-1 and -2 as mol. targets for γ -secretase inhibitors:
cell membrane binding)

IT 76944-95-1

RL: RCT (Reactant); RACT (Reactant or reagent)
(presenilin-1 and -2 as mol. targets for γ -secretase inhibitors:
cell membrane binding)

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L34 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:5300 HCAPLUS

DN 132:135959

ED Entered STN: 04 Jan 2000

TI Overexpression of the neuritotrophic cytokine S100 β precedes the appearance of neuritic β -amyloid plaques in APPV717F mice

AU Sheng, J. G.; Mrak, R. E.; Bales, K. R.; Cordell, B.; Paul, S.

M.; Jones, R. A.; Woodward, S.; Zhou, X. Q.; McGinness, J. M.; Griffin, W. S. T.

CS Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA

SO Journal of Neurochemistry (2000), 74(1), 295-301
CODEN: JONRA9; ISSN: 0022-3042

PB Lippincott Williams & Wilkins

DT Journal

LA English

CC 14-10 (Mammalian Pathological Biochemistry)

AB Homozygous APPV717F transgenic mice overexpress a human β -amyloid precursor protein (.beta.APP) minigene encoding a familial Alzheimer's disease mutation. These mice develop Alzheimer-type neuritic β -amyloid plaques surrounded by astrocytes. S100 β is an astrocyte-derived cytokine that promotes neurite growth and promotes excessive expression of .beta.APP. S100 β overexpression in Alzheimer's disease correlates with the proliferation of .beta.APP-immunoreactive neurites in β -amyloid plaques. The authors found age-related increases in tissue levels of both .beta.APP and S100 β mRNA in transgenic mice. Neuronal .beta.APP overexpression was found in cell somas in young mice, whereas older mice showed .beta.APP overexpression in dystrophic neurites in plaques. These age-related changes were accompanied by progressive increases in S100 β expression, as determined by S100 β load (percent immunoreactive area). These increases were evident as early as 1 and 2 mo of age, months before the appearance of β -amyloid deposits in these mice. Such precocious astrocyte activation and S100 β overexpression are similar to the authors' earlier findings in Down's syndrome. Accelerated age-related overexpression of S100 β may interact with age-associated overexpression of mutant .beta.APP in transgenic mice to promote development of Alzheimer-like neuropathol. changes.

ST neuritotrophic cytokine S100beta amyloid plaque

IT **Alzheimer's disease**
(familial; overexpression of neuritotrophic cytokine S100 β precedes neuritic β -amyloid plaques development in model of)

IT **Astrocyte**
(neuritic β -amyloid plaques development is associated with S100 β overexpression by)

IT **Brain, disease**
(senile plaque; overexpression of neuritotrophic cytokine S100 β precedes neuritic β -amyloid plaques development in Alzheimer model)

IT **Amyloid**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β -; overexpression of neuritotrophic cytokine S100 β precedes neuritic β -amyloid plaques development in Alzheimer model)

RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Barger, S; Nature 1997, V388, P878 HCAPLUS
- (2) Buxbaum, J; Proc Natl Acad Sci 1992, V89, P10075 HCAPLUS
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L34 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:674911 HCAPLUS

DN 132:21804

ED Entered STN: 24 Oct 1999

TI Presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons

AU Annaert, Wim G.; Levesque, Lyne; Craessaerts, Kathleen; Dierinck, Inge; Snellings, Greet; Westaway, David; St. George-Hyslop, Peter; Cordell, Barbara; Fraser, Paul; De Strooper, Bart

CS CME/VIB4/KULeuven, Louvain, B-3000, Belg.

SO Journal of Cell Biology (1999), 147(2), 277-294

CODEN: JCLBA3; ISSN: 0021-9525

PB Rockefeller University Press

DT Journal

LA English

CC 14-10 (Mammalian Pathological Biochemistry)

AB Mutations of presenilin 1 (PS1) causing Alzheimer's disease selectively increase the secretion of the amyloidogenic β A4(1-42), whereas knocking out the gene results in decreased production of both β A4(1-40) and (1-42) amyloid peptides (De Strooper, B.; et al., 1998). Therefore, PS1 function is closely linked to the γ -secretase processing of the amyloid precursor protein (APP). Given the ongoing controversy on the subcellular localization of PS1, it remains unclear at what level of the secretory and endocytic pathways PS1 exerts its activity on APP and on the APP carboxy-terminal fragments that are the direct substrates for γ -secretase. Therefore, we have reinvestigated the subcellular localization of endogenously expressed PS1 in neurons in vitro and in vivo using confocal microscopy and fine-tuned subcellular fractionation. We show that uncleaved PS1 holoprotein is recovered in the nuclear envelope fraction, whereas the cleaved PS fragments are found mainly in post-ER membranes including the intermediate compartment (IC). PS1 is concentrated in discrete sec23p- and p58/ERGIC-53-pos. patches, suggesting its localization in subdomains involved in ER export. PS1 is not found to significant amts. beyond the cis-Golgi. Surprisingly, we found that APP carboxy-terminal fragments also coenrich in the pre-Golgi membrane fractions, consistent with the idea that these fragments are the real substrates for γ -secretase. Functional evidence that PS1 exerts its effects on γ -secretase processing of APP in the ER/IC was obtained using a series of APP trafficking mutants. These mutants were investigated in hippocampal neurons derived from transgenic mice expressing PS1wt or PS1 containing clin. mutations (PS1M146L and PS1L286V) at physiol. relevant levels. We demonstrate that the APP-London and PS1 mutations have additive effects on the increased secretion of β A4(1-42) relative to β A4(1-40), indicating that both mutations operate independently. Overall, our data clearly establish that PS1 controls γ 42-secretase activity in pre-Golgi compartments. We discuss models that reconcile this conclusion with the effects of PS1 deficiency on the generation of β A4(1-40) peptide in the late biosynthetic and endocytic pathways.

ST presenilin secretase amyloid precursor protein hippocampus neuron

- IT **Presenilins**
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (1; presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Golgi apparatus
 (cis-, presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Cell nucleus
 (envelope; presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Alzheimer's disease
 (familial; presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Brain
 (hippocampus; presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Nerve
 (neuron; presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Organelle
 (pre-Golgi compartment; presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Alzheimer's disease
 Endoplasmic reticulum
 (presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT Amyloid precursor proteins
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT 107761-42-2, Glycopeptide (human clone 9-110 amyloid A4 peptide moiety) 131438-79-4
 RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)
- IT 158736-49-3, γ -Secretase
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (presenilin 1 controls γ -secretase processing of amyloid precursor protein in pre-golgi compartments of hippocampal neurons)

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L34 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1999:529819 HCAPLUS

DN 131:295102

ED Entered STN: 25 Aug 1999

TI A Combinatorial Approach to the Identification of Dipeptide Aldehyde Inhibitors of β -Amyloid Production

AU Higaki, Jeffrey N.; Chakravarty, Sarvajit; Bryant, Carmen M.; Cowart, Lisa R.; Harden, Paul; Scardina, Jan Marian; Mavunkel, Babu; Luedtke, Gregory R.; Cordell, Barbara

CS Scios Inc., Sunnyvale, CA, 94086, USA

SO Journal of Medicinal Chemistry (1999), 42(19), 3889-3898

CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

CC 1-3 (Pharmacology)

Section cross-reference(s): 13, 34

AB In an effort to rapidly identify potent inhibitors of A β production and to probe the amino acid sequence specificity of the protease(s) responsible for the production of this peptide, a large number of dipeptide aldehydes were combinatorially synthesized and manually evaluated for their inhibitory properties. The starting point for this study was the dipeptide aldehyde carbobenzoxyl-valinyl-phenylalanyl previously shown to inhibit the production of A β in CHO cells stably transfected with the cDNA encoding .beta.APP695. Pools of related dipeptide aldehydes were combinatorially synthesized, and the most active pool was deconvoluted, resulting in the identification of the most active inhibitor of this pool. Systematic optimization of this inhibitor resulted in a series of dipeptide aldehydes with enhanced potencies relative to carbobenzoxyl-valinyl-phenylalanyl. The most active dipeptide aldehydes were those that possessed hydrophobic amino acids at both the P1 and P2 positions. The most potent compound identified in this study was 3,5-dimethoxycinnamamide-isoleucinyl-leucinal with an IC50 of 9.6 μ M, approx. 10-fold more active than carbobenzoxyl-valinyl-phenylalanyl. In immunopptn. expts. using antibodies directed toward either A β 1-40 or A β 1-42, 3,5-dimethoxycinnamamide-isoleucinyl-leucinal, like carbobenzoxyl-valinyl-phenylalanyl, preferentially inhibited the shorter 1-40 form of A β , whereas the longer 1-42 form was not as strongly inhibited. These results suggest that dipeptide aldehydes related to carbobenzoxyl-valinyl-phenylalanyl inhibit A β through similar mechanisms and demonstrate the utility of a combinatorial synthesis approach to rapidly identify potent inhibitors of A β production

ST beta amyloid prodn dipeptide aldehyde structure; combinatorial dipeptide aldehyde library amyloid prodn; secretase beta amyloid prodn dipeptide aldehyde

IT Peptide library
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT Aldehydes, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(peptide aldehydes; combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT Amyloid

RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(β -; combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT Structure-activity relationship

(β -amyloid production-inhibiting; combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT 88191-84-8 247021-87-0

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT 593-56-6 1663-39-4 28920-43-6, Fmoc-chloride

RL: RCT (Reactant); RACT (Reactant or reagent)
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT 247021-88-1P 247021-89-2P 247021-90-5DP, conjugates with methoxybenzhydrylamine resin 247021-90-5DP, conjugates with methoxybenzhydrylamine resin

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

IT 158736-49-3, γ -Secretase

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -amyloid production by; combinatorial approach to identification of dipeptide aldehyde inhibitors of β -amyloid production)

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L34 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1998:605021 HCAPLUS

DN 129:198885

ED Entered STN: 24 Sep 1998

TI Animal cell lines manufacturing β -amyloid and their use in the screening for drugs affecting its processing and accumulation

IN Cordell, Barbara; Scardina, Jan Marian; Mischak, Ronald P.;

Huggins, John; Pruss, Rebecca; Rautmann, Guy

PA Hoechst Marion Roussel, Inc., USA; Scios Inc.

SO PCT Int. Appl., 83 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N015-85

ICS C12N015-12; C12N005-10; C07K014-47; G01N033-68; C07K016-18

CC 3-2 (Biochemical Genetics)

Section cross-reference(s): 1

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9837215	A1	19980827	WO 1998-US1899	19980203
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
	AU 9862600	A1	19980909	AU 1998-62600	19980203
	EP 973923	A1	20000126	EP 1998-904812	19980203
	R:	CH, DE, FR, GB, IT, LI			
	JP 2001512973	T2	20010828	JP 1998-536647	19980203
	ZA 9801387	A	19980824	ZA 1998-1387	19980219
PRAI	US 1997-804971	A	19970224		
	US 1997-825737	A	19970402		
	US 1997-904296	A	19970731		
	WO 1998-US1899	W	19980203		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9837215	ICM	C12N015-85
	ICS	C12N015-12; C12N005-10; C07K014-47; G01N033-68; C07K016-18
WO 9837215	ECLA	C07K014/47A3

AB Eukaryotic cell lines useful in the identification of inhibitors of β -amyloid processing are designed and constructed. More specifically, the invention relates to in vitro assays capable of

identifying or quantifying a 4.2 kDa β -amyloid protein. A vector for high-level expression of a cDNA for the 695 amino acid isoform of amyloid precursor (APP695) was cloned and placed under control of the cytomegalovirus immediate-early promoter. CHO cells transformed with the expression construct were screened for high levels of production of APP695 and β -amyloid. High producers were further studied to identify the patterns of accumulation of processing products. Lines yielding ≥ 70 ng β -amyloid/mg protein were obtained. Characterization of patterns of processing can be used to identify agents affecting processing.

- ST beta amyloid processing cells high yield; amyloid processing cells inhibitor screening
- IT **Amyloid precursor proteins**
 RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
 (APP695, cloning and expression of cDNA for, processing of; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Gene, animal
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
 (CAD, as selectable marker; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Animal cell line
 (CHO, expression host; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Genetic element
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
 (IRES (internal ribosomal entry site) element, in expression construct for β -amyloid precursor; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT **Alzheimer's disease**
 Animal cell line
 Drug screening
 (animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Kidney
 (cell lines of human, as expression host; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Hamster
 (cell lines of, as expression host; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Immunoassay
 (enzyme-linked immunosorbent assay, for β -amyloid; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Encephalomyocarditis virus
 (expression vectors using IRES element of; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Gene, animal
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
 (for β -amyloid precursor, cloning and expression of; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Neuroglia
 (glioma, cell lines of, as expression host; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its

- processing and accumulation)
- IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(immediate early, APP695 cDNA expression from; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Antibodies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(monoclonal, to β -amyloid; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Nerve, neoplasm
(neuroblastoma, cell lines of, as expression host; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Post-translational processing
(of β -amyloid; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Plasmid vectors
(pCMV-IRES- β APP695, cDNA for amyloid precursor protein 695-amino acid isoform on; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Amyloid precursor proteins
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(processing of; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Immunoassay
(radioimmunoassay, for β -amyloid; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Antibodies
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to β -amyloid; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(β -; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT 3654-96-4, L-Methionine-35S 24321-12-8, L-Cysteine-35S
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(as label for monitoring of amyloid precursor processing; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)
- IT 9002-06-6, Thymidine kinase 9012-49-1, Aspartate transcarbamylase 9023-69-2, Asparagine synthase 9023-70-5, Glutamine synthase 9024-60-6, Ornithine decarboxylase 9026-93-1, Adenosine deaminase 37350-22-4, Xanthine-guanine phosphoribosyltransferase 56941-28-7, Aminoglycoside phosphotransferase 62213-36-9, Neomycin phosphotransferase 74870-74-9, UMP synthetase 88361-67-5, Hygromycin B phosphotransferase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for, as selectable marker; animal cell lines manufacturing β -amyloid and their use in screening for drugs affecting its processing and accumulation)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L34 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1998:239357 HCAPLUS
 DN 128:278968
 ED Entered STN: 27 Apr 1998
 TI Method to identify direct inhibitors of the beta-amyloid forming enzyme
 gamma-secretase
 IN Cordell, Barbara; Higaki, Jeffrey N.
 PA Scios Inc., USA; Cordell, Barbara; Higaki, Jeffrey N.
 SO PCT Int. Appl., 31 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM G01N033-50
 ICS G01N033-68
 CC 1-1 (Pharmacology)
 Section cross-reference(s): 9

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9815828	A1	19980416	WO 1997-US16988	19970919
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9745892	A1	19980505	AU 1997-45892	19970919
PRAI	US 1996-726524	A	19961007		
	WO 1997-US16988	W	19970919		

CLASS

	PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
	WO 9815828	ICM	G01N033-50
		ICS	G01N033-68
	WO 9815828	ECLA	G01N033/50D2; G01N033/68V2
AB	A method for identifying direct inhibitors of γ -secretase is described. A cell line expressing β -APP is cultured in contact with a compound known to inhibit γ -secretase activity, thereby causing accumulation of β -APP carboxyl-terminal fragments in the cell. The known γ -secretase inhibiting compound is removed and replaced with a test substance. The direct γ -secretase inhibitory activity of the test substance is determined by quantifying the amount of β -APP carboxyl-terminal fragments in the cells and/or quantifying the amount of β -amyloid peptide in the culture medium over time.		
ST	gamma secretase inhibitor beta amyloid; Alzheimer beta amyloid gamma secretase inhibitor		
IT	Animal tissue culture		
	Anti-Alzheimer's agents (method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase)		
IT	Amyloid RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (β -; method to identify direct inhibitors of the beta-amyloid forming enzyme gamma-secretase)		
IT	88191-84-8, MDL 28170 RL: BAC (Biological activity or effector, except adverse); BSU (Biological		

study, unclassified); BIOL (Biological study)
 (method to identify direct inhibitors of the beta-amyloid forming
 enzyme gamma-secretase)

IT 158736-49-3, γ -Secretase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (method to identify direct inhibitors of the beta-amyloid forming
 enzyme gamma-secretase)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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- (2) Ho, L; J BIOL CHEM 1996, V271(48), P30929 HCAPLUS
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L34 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1997:21581 HCAPLUS

DN 126:155938

ED Entered STN: 15 Jan 1997

TI Processing of β -amyloid precursor protein by cathepsin D

AU Higaki, Jeffrey; Catalano, Rosanne; Guzzetta, Andrew W.; Quon,
 Diana; Nave, Jean-Francois; Tarnus, Celine; D'Orchymont, Hugues;
 Cordell, Barbara

CS Scios, Inc., Mountain View, CA, 94043, USA

SO Journal of Biological Chemistry (1996), 271(50), 31885-31893
 CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 14-10 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 7

AB The events leading to the formation of β -amyloid (β A4) from its
 precursor (.beta.APP) involve proteolytic cleavages
 that produce the amino and carboxyl termini of β A4. The enzyme
 activities responsible for these cleavages have been termed β - and
 γ -secretase, resp., although these protease(s) have not been
 identified. Since β A4 is known to possess heterogeneity at both the
 amino and carboxyl termini, β - and γ -secretases may actually be
 a collection of proteolytic activities or perhaps a single proteolytic
 enzyme with broad amino acid specificity. The authors investigated the
 role of cathepsin D in the processing of .beta.APP
 since this enzyme has been widely proposed as a γ -secretase
 candidate. Treatment of a synthetic peptide that spans the
 γ -secretase site of .beta.APP with human
 cathepsin D resulted in the cleavage of this substrate at Ala42-Thr43. A
 sensitive liquid chromatog./mass spectrometry technique was also developed
 to further investigate the ability of cathepsin D to process longer
 recombinant .beta.APP substrates (156 and 100 amino
 acids of .beta.APP carboxyl terminus) in vitro. The
 precise cathepsin D cleavage sites within these recombinant .beta
 .APP substrates were identified using this technique. Both
 recombinant substrates were cleaved at the following sites: Leu49-Val50,
 Asp68-Ala69, Phe93-Phe94. No cleavages were observed at putative
 γ -secretase sites: Val40-Ile41 or Ala42-Thr43, suggesting that
 cathepsin D is not γ -secretase as defined by these β A4 termini.
 Under conditions where the .beta.APP156 substrate was
 first denatured prior to cathepsin D digestion, two addnl. cleavage sites
 near the amino terminus of β A4, Glu-3-Val-2 and Glu3-Phe4, were
 observed, indicating that cathepsin D cleavage of .beta.APP
 is influenced by the structural integrity of the substrate. Taken
 together, these results indicate that in vitro, cathepsin D is unlikely to
 function as γ -secretase; however, the ability of this enzyme to
 efficiently cleave .beta.APP substrates at
 nonamyloidogenic sites within the mol. may reflect a role in .beta

- .APP catabolism.
- ST beta amyloid precursor protein cathepsin D; Alzheimer beta amyloid precursor cathepsin D
- IT **Alzheimer's disease**
Protein degradation
(processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT **Amyloid precursor proteins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT **Amyloid**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(β -; processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT 106096-93-9DP, Basic fibroblast growth factor, fusion protein with β -amyloid precursor protein APP751 and FLAG peptide 186795-27-7P 186847-25-6P
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(preparation of; processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT 148125-60-4DP, Proteinase inhibitor, protease-nexin II, fusion protein with FLAG peptide and basic fibroblast growth factor
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of; processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT 186847-24-5P
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of; processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT 9025-26-7, Cathepsin D
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)
- IT 158736-49-3, γ -Secretase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(processing of β -amyloid precursor protein by human cathepsin D in relation to γ -secretase)

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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L34 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1996:556391 HCAPLUS

DN 125:244059

ED Entered STN: 18 Sep 1996

TI β -Amyloid precursor protein. Location of transmembrane domain and specificity of γ -secretase cleavage

AU Tischer, Edmund; Cordell, Barbara

CS Scios Inc., Mountain View, CA, 94043, USA

SO Journal of Biological Chemistry (1996), 271(36), 21914-21919

CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 13-6 (Mammalian Biochemistry)

Section cross-reference(s): 6

AB The formation of β -amyloid by processing of its precursor protein is a characteristic of Alzheimer's disease. Two proteolytic cleavages produce the amino and carboxyl termini of β -amyloid, with the latter cleavage site located within the transmembrane domain. Using DNA mutagenesis, the authors investigated the membrane position and sequence requirements for carboxyl-terminal processing of the β -amyloid domain. Substitution of neg. charged residues across positions 40-46 of the β -amyloid domain precluded both β -amyloid formation and precursor maturation associated with secretory protein transport. In contrast, identical substitutions from positions 48-50 had no adverse effects. Since charged residues typically prevent protein membrane insertion, these data define the membrane boundary to position 46/47, a location allowing greater access to carboxyl-terminal processing of β -amyloid, possibly without membrane destruction. Deletions within the carboxyl-terminal domain, including 4 residues spanning positions 39-42 of β -amyloid, resulted in formation of the β -amyloid

peptide. Substituting residues 38-47 or 39-56 or the β -amyloid domain in the precursor with a transmembrane sequence from another protein yielded a .apprx.4kDa β -amyloid peptide, reflecting a loose residue specificity for carboxyl-terminal processing to β -amyloid.

ST beta amyloid precursor protein processing secretase

IT Protein sequences

(in β -amyloid precursor protein transmembrane domain for γ -secretase cleavage)

IT Molecular structure-biological activity relationship

(β -amyloid precursor protein transmembrane domain and specificity of γ -secretase cleavage in relation to β -amyloid formation)

IT Mental disorder

(Alzheimer's disease, β -amyloid precursor protein transmembrane domain and specificity of γ -secretase cleavage in relation to β -amyloid formation)

IT Proteins, specific or class

RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(amyloid A4, β -amyloid precursor protein transmembrane domain and specificity of γ -secretase cleavage in relation to β -amyloid formation)

IT Glycoproteins, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(amyloid A4, pre-, β -amyloid precursor protein transmembrane domain and specificity of γ -secretase cleavage in relation to β -amyloid formation)

IT 158736-49-3, γ -Secretase

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(β -amyloid precursor protein transmembrane domain and specificity of γ -secretase cleavage in relation to β -amyloid formation)

L34 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1996:208278 HCAPLUS

DN 124:285462

ED Entered STN: 11 Apr 1996

TI A model of β -amyloid formation and Alzheimer's disease

AU Cordell, Barbara; Higgins, Linda S.; Higaki, Jeffrey; Zhong, Ziyang; Moran, Paula M.; Moser, Paul M.

CS Scios Nova Inc., Mountain View, CA, 94043, USA

SO Alzheimer's Research (1995), 1(3), 111-15

CODEN: ALREFFB; ISSN: 1356-918X

PB Rapid Science Publishers

DT Journal; General Review

LA English

CC 14-0 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 13

AB A review with 25 refs. The influence of a single gene can be evaluated in vitro and in vivo through mol. genetics. The authors have applied this approach to study β -amyloid formation and Alzheimer's disease. The gene under exptl. assessment was that encoding the human β -amyloid precursor protein (β -APP). The authors examined the pathol. influence of β -APP gene expression in cultured mammalian cells and transgenic mice. From the in vitro studies, the authors found that increased β -amyloid formation was associated with increased expression of β -APP and/or aberrant . beta.-APP mols. Hence, the authors hypothesized that β -amyloid is a minor degradative byproduct of β -APP catabolism. This hypothesis was exptl. supported at the in vivo level using transgenesis. Transgenic mice aberrantly expressing . beta.-APP in their neurons were shown to display histol. and behavioral features analogous to those observed in early Alzheimer's disease. These features included extracellular diffuse deposits of β -amyloid derived from the exogenous gene, aberrancies in the neuronal cytoskeleton, as well as memory and learning impairments. The

phenotype of this transgenic mouse indicates a central role for .
beta.-APP in the pathogenesis of Alzheimer's disease and
 supports the hypothesis of β -amyloid formation.

ST review beta amyloid formation Alzheimer disease

IT Mouse

(transgenic; β -amyloid formation in pathogenesis of Alzheimer's
 disease using transgenic mouse model)

IT Mental disorder

(Alzheimer's disease, β -amyloid formation in pathogenesis of
 Alzheimer's disease using transgenic mouse model)

IT **Proteins, specific or class**

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM
 (Formation, nonpreparative)

(**amyloid A4**, β -amyloid formation in
 pathogenesis of Alzheimer's disease using transgenic mouse model)

IT Transformation, genetic

(transgenic, β -amyloid formation in pathogenesis of Alzheimer's
 disease using transgenic mouse model)

L34 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1995:617282 HCAPLUS

DN 123:53503

ED Entered STN: 16 Jun 1995

TI Age-related learning deficits in transgenic mice expressing the 751-amino
 acid isoform of human β -amyloid precursor protein

AU Moran, Paula M.; Higgins, Linda S.; Cordell, Barbara; Moser,
 Paul C.

CS Marion Merrell Dow Research Inst., Strasbourg, 67080, Fr.

SO Proceedings of the National Academy of Sciences of the United States of
 America (1995), 92(12), 5341-5
 CODEN: PNASA6; ISSN: 0027-8424

PB National Academy of Sciences

DT Journal

LA English

CC 14-10 (Mammalian Pathological Biochemistry)

AB The β -amyloid precursor protein (β -APP),
 from which the β -A4 peptide is derived, is considered to be central
 to the pathogenesis of Alzheimer disease (AD). Transgenic mice expressing
 the 751-amino acid isoform of human β -APP (.
beta.-APP751) have been shown to develop early AD-like
 histopathol. with diffuse deposits of β -A4 and aberrant tau protein
 expression in the brain, particularly in the hippocampus, cortex, and
 amygdala. The authors now report that β -APP751
 transgenic mice exhibit age-dependent deficits in spatial learning in a
 water-maze task and in spontaneous alternation in a Y maze. These
 deficits were mild or absent in 6-mo-old transgenic mice but were severe
 in 12-mo-old transgenic mice compared to age-matched wild-type control
 mice. No other behavioral abnormalities were observed These mice therefore
 model the progressive learning and memory impairment that is a cardinal
 feature of AD. These results provide evidence for a relation between
 abnormal expression of β -APP and cognitive
 impairments.

ST amyloid precursor protein 751 Alzheimer disease

IT Brain

Senescence

(age-related learning deficits in transgenic mice expressing the
 751-amino acid isoform of human β -amyloid precursor protein)

IT Mental disorder

(Alzheimer's disease, age-related learning deficits in transgenic mice
 expressing the 751-amino acid isoform of human β -amyloid precursor
 protein)

IT Learning

Memory, biological

(disorder, age-related learning deficits in transgenic mice expressing
 the 751-amino acid isoform of human β -amyloid precursor protein)

IT Behavior
(spontaneous alternation, age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β -amyloid precursor protein)

IT 148125-60-4, Glycoproteins, specific or class, amyloid A4751
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(age-related learning deficits in transgenic mice expressing the 751-amino acid isoform of human β -amyloid precursor protein)

L34 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:562704 HCAPLUS
DN 123:30662
ED Entered STN: 20 May 1995
TI Early Alzheimer disease-like histopathology increases in frequency with age in mice transgenic for β -APP751
AU Higgins, L. S.; Rodems, J. M.; Catalano, R.; Quon, D.; Cordell, B.
CS Scios Nova Inc., Mountain View, CA, 94043, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1995), 92(10), 4402-6
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB β -Amyloid deposition and neurofibrillary tangle formation are 2 histopathol. features of Alzheimer disease. The authors previously reported that β -amyloid immunoreactive deposits form in the brains of transgenic mice programmed for neuronal expression of the 751-amino acid isoform of human β -amyloid precursor protein (β -APP751) and now describe that these animals also display Alz50 intraneuronal immunoreactivity similar to that seen in early Alzheimer disease. This suggests that abnormal β -APP expression and/or β -amyloid deposition promotes pathogenic alterations in tau protein. The frequency of both β -amyloid deposition and Alz50-pos. neurons was twice as prevalent in brains from old (22 mo) as compared to young (2-3 mo) β -APP751 transgenic mice. This increase in histopathol. with age in .beta .-APP751 transgenic mice parallels the time-dependent progression seen in the human disease.
ST amyloid Alz50 Tau Alzheimer transgenic mouse
IT Senescence
(Alzheimer disease-like histopathol. increases in frequency with age in mice transgenic for β -APP751)

IT Glycoproteins, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(amyloid A4751; β -amyloid deposits and Alz50-pos. neurons of β -APP751 transgenic mice increase with age)

IT Tau factors
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β -amyloid deposits and Alz50-pos. neurons in β -APP751 transgenic mice increase with age)

IT Antigens
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(Alz-50, β -amyloid deposits and Alz50-pos. neurons in β -APP751 transgenic mice increase with age)

IT Mental disorder
(Alzheimer's disease, β -amyloid deposits and Alz50-pos. neurons in β -APP751 transgenic mice increase with age)

IT Proteins, specific or class
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(amyloid A4, β -amyloid deposits and Alz50-pos. neurons of β -APP751 transgenic mice increase with age)

IT Brain, disease

(neurofibrillary tangle, β -amyloid deposits and Alz50-pos. neurons in β -APP751 transgenic mice increase with age)

IT Brain, disease

(senile plaque, β -amyloid deposits and Alz50-pos. neurons in β -APP751 transgenic mice increase with age)

L34 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 1995:483374 HCAPLUS

DN 122:236925

ED Entered STN: 12 Apr 1995

TI Inhibition of β -amyloid formation identified proteolytic precursors and subcellular site of catabolism

AU Higaki, Jeffrey; Quon, Diana; Zhong, Ziyang; Cordell, Barbara

CS Scios Nova, Inc., Mountain View, CA, 94043, USA

SO Neuron (1995), 14(3), 651-9

CODEN: NERNET; ISSN: 0896-6273

PB Cell Press

DT Journal

LA English

CC 14-10 (Mammalian Pathological Biochemistry)

AB Cerebral deposition of β -amyloid protein is a pathol. feature central to Alzheimer's disease. Production of β -amyloid by proteolytic processing of the β -amyloid precursor protein (β APP) is a critical initial step in β -amyloidogenesis. We use an inhibitor of .beta.APP processing to block β -amyloid peptide formation. Application of the inhibitor to cultured cells results in an accumulation of proteolytic intermediates of .beta.APP, enabling a precursor-product relationship between .beta.APP carboxy-terminal fragments and β -amyloid peptides to be demonstrated directly. In the presence of inhibitor, these amyloidogenic carboxy-terminal fragments can be degraded to nonamyloidogenic products. The catabolism of β APP carboxy-terminal intermediates and the formation of β -amyloid peptides are likely to involve an early endosomal compartment as the subcellular site of processing.

ST beta amyloid precursor protein endosome catabolism; Alzheimer disease beta amyloid accumulation

IT Down's syndrome

(catabolism of β -amyloid precursor protein in endosomal compartment results in β -amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)

IT Mental disorder

(Alzheimer's disease, catabolism of β -amyloid precursor protein in endosomal compartment results in β -amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)

IT Proteins, specific or class

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(amyloid A4, catabolism of β -amyloid precursor protein in endosomal compartment results in β -amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)

IT - Glycoproteins, specific or class

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(amyloid A4, pre-, catabolism of β -amyloid precursor protein in endosomal compartment results in β -amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)

IT Organelle

(endocytic vesicle, catabolism of β -amyloid precursor protein in endosomal compartment results in β -amyloid formation and accumulation in Alzheimer's disease and Down's syndrome)

L34 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1994:480134 HCAPLUS
 DN 121:80134
 ED Entered STN: 20 Aug 1994
 TI Increased amyloid production from aberrant β -amyloid precursor proteins
 AU Zhong, Ziyang; Quon, Diana; Higgins, Linda S.; Higaki, Jeffrey; Cordell, Barbara
 CS Scios Nova Inc., Mountain View, CA, 94043, USA
 SO Journal of Biological Chemistry (1994), 269(16), 12179-84
 CODEN: JBCHA3; ISSN: 0021-9258
 DT Journal
 LA English
 CC 14-10 (Mammalian Pathological Biochemistry)
 Section cross-reference(s): 13
 AB The 4-kDa β -amyloid protein that forms fibrillar deposits in Alzheimer's diseased brains is derived from a large precursor, the β -amyloid precursor protein (β -APP). Recently, it has been reported that β -amyloid is normally produced and secreted by cultured mammalian cells. In the authors' studies involving recombinant expression of β -APP, increased yields of β -amyloid were associated with expression of aberrant β -APP mols. Deletion mutations within the β -amyloid domain, incorrect β -APP isoform expression in fibroblasts or neuronal cells, or excess amts. of β -APP all led to increases in β -amyloid production. Aberrant β -APP appears to be diverted from the secretory pathway and then degraded to β -amyloid.
 ST aberrant beta amyloid precursor processing Alzheimer
 IT Fibroblast
 Nerve, metabolism
 (aberrant β -amyloid precursor proteins of, β -amyloid protein formation response to)
 IT Mental disorder
 (Alzheimer's disease, β -amyloid formation from aberrant β -amyloid precursor proteins in relation to, in fibroblasts and neuron cells)
 IT Proteins, specific or class
 RL: FORM (Formation, nonpreparative)
 (amyloid A4, formation of, fibroblasts and neuronal cell aberrant β -amyloid precursor proteins stimulation of)
 IT Glycoproteins, specific or class
 RL: BIOL (Biological study)
 (amyloid A4, pre-, aberrant forms of, in fibroblasts and neuronal cells, β -amyloid protein formation response to)

L34 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1994:74682 HCAPLUS
 DN 120:74682
 ED Entered STN: 19 Feb 1994
 TI Secretion of β -amyloid precursor protein involves multiple cleavage sites
 AU Zhong, Ziyang; Higaki, Jeffrey; Murakami, Kenji; Wang, Yu; Catalano, Rosanne; Quon, Diana; Cordell, Barbara
 CS Scios Nova Inc., Mountain View, CA, 94043, USA
 SO Journal of Biological Chemistry (1994), 269(1), 627-32
 CODEN: JBCHA3; ISSN: 0021-9258
 DT Journal
 LA English
 CC 14-10 (Mammalian Pathological Biochemistry)
 AB A major histopathol. feature of Alzheimer's disease is deposition of a .apprx.4-kDa β -amyloid peptide derived by proteolytic processing from a precursor, the β -amyloid precursor protein (β -APP). Proteolytic cleavage of β -APP

within the .apprx.4-kDa β -amyloid domain permits the secretion of the amino-terminal portion of β -APP while concomitantly producing a membrane bound .apprx.9-kDa carboxyl-terminal fragment. The authors have characterized the proteolytic cleavage site for β -APP secretion by amino acid sequence anal. of the .apprx.9-kDa β -APP carboxyl-terminal cleavage product produced by recombinant and native expression systems. Recombinant β -APP was generated by a vaccinia virus expression system in CV-1 monkey fibroblasts; endogenous β -APP was obtained using a fibroblast line derived from an individual with Down's syndrome. The sequences of both unlabeled and metabolically radiolabeled .apprx.9-kDa fragment from CV-1 cells reveal that the major (60%) secretory cleavage site is after Lys16 of the β -amyloid domain as reported previously; however, an addnl. cleavage site is seen after Phe19 (40%). Radiosequence anal. of the carboxyl-terminal fragment purified from Down's syndrome fibroblasts indicates cleavage sites after Phe19, Glu22, and Gly25 and not after Lys16. CV-1 cells expressing β -APP mutants lacking 4 and 6 amino acids adjacent to Lys16 yielded .apprx.9-kDa fragments with two identical cleavage sites, neither of which occurred after the retained Lys16 but were after Glu11 and His13. These data suggest that secretion of β -APP involves multiple proteinases and that the composition of these proteinases may vary within different cell backgrounds.

ST amyloid precursor protein processing proteinase Alzheimer
IT Mental disorder
(Alzheimer's disease, β -amyloid precursor protein processing by multiple proteinases and cleavage site identification in relation to)
IT Glycoproteins, specific or class
RL: BIOL (Biological study)
(amyloid A4, pre-, processing of, by multiple proteinases, cleavage site identification in, Alzheimer's disease in relation to)
IT 9001-92-7, Proteinase
RL: BIOL (Biological study)
(β -amyloid precursor protein processing by, cleavage site identification in, Alzheimer's disease in relation to)

L34 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:676982 HCAPLUS
DN 115:276982
ED Entered STN: 27 Dec 1991
TI Alzheimer's disease: β -amyloid precursor protein expression in plaques varies among cytoarchitectonic areas of the medial temporal lobe
AU Murphy, Greer M., Jr.; Murphy, Erin; Greenberg, Barry D.; Cordell, Barbara; Eng, Lawrence F.; Ellis, William G.; Forno, Lysia S.; Salamat, Shahriar M.; Gonzalez-DeWhitt, Patricia A.; et al.
CS Sch. Med., Stanford Univ., Palo Alto, CA, 94304, USA
SO Neuroscience Letters (1991), 131(1), 100-4
CODEN: NELED5; ISSN: 0304-3940
DT Journal
LA English
CC 14-10 (Mammalian Pathological Biochemistry)
AB The anat. distributions of β -amyloid peptide (β AP) and β -amyloid precursor protein (β -APP) in the medial temporal lobe were examined with immunocytochem. in Alzheimer's disease. β AP-containing plaques were found most frequently in the cortical and basal regions of the amygdala, and in the hippocampal CA1, subiculum, and dentate mol. layer. β -APP expression in plaques was found in a similar distribution, with some, but not all β AP plaques also showing β -APP. In the cortical and basal amygdala, some cases showed β -APP in the centers of plaques, whereas in the hippocampus, all cases displayed β -APP mainly in plaque neurites. The lateral regions of the amygdala contained mainly diffuse β AP plaques which had little β -APP. These findings

suggest that although .beta.APP expression and
 betaAP deposition generally co-localize, processing of beta
 APP may vary among closely interconnected anat. regions.

ST amyloid precursor protein plaque brain Alzheimer
 IT Mental disorder
 (Alzheimer's disease, beta-amyloid precursor protein of neuritic
 plaques of brain regions in, of humans)

IT Glycoproteins, specific or class
 RL: BIOL (Biological study)
 (amyloid A4, pre-, of neuritic plaques,
 of brain regions, in Alzheimer's disease of humans)

IT Brain, composition
 (neuritic plaque, beta-amyloid precursor protein of, in Alzheimer's
 disease of humans)

L34 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1991:512097 HCAPLUS
 DN 115:112097
 ED Entered STN: 23 Sep 1991
 TI Formation of beta-amyloid protein deposits in brains of transgenic mice
 AU Quon, D.; Wang, Y.; Catalano, R.; Scardina, J. Marian; Murakami,
 K.; Cordell, B.
 CS California Biotechnol. Inc., Mountain View, CA, 94043, USA
 SO Nature (London, United Kingdom) (1991), 352(6332), 239-41
 CODEN: NATUAS; ISSN: 0028-0836
 DT Journal
 LA English
 CC 14-10 (Mammalian Pathological Biochemistry)
 AB Deposits of beta-amyloid are one of the main pathol. characteristics of
 Alzheimer's disease. The beta-amyloid peptide constituent (relative
 mol. mass 4,200) of the deposits is derived from the beta-amyloid
 precursor protein (beta -APP) which is expressed in
 several different isoforms. The two most prevalent beta -
 APP isoforms are distinguished by either the presence (.
 beta.-APP751) or absence (beta -
 APP695) of a Kunitz serine protease inhibitor domain. Changes in
 the abundance of different beta -APP mRNAs in brains
 of Alzheimer's disease victims have been widely reported. Although these
 results have been controversial, most evidence favors an increase in the
 mRNAs encoding protease inhibitor-containing isoforms of B-APP and it is
 proposed that this change contributes to B-amyloid formation. The authors
 have now produced an imbalance in the normal neuronal ratio of .
 beta.-APP isoforms by preparing transgenic mice expressing
 addnl. beta -APP751 under the control of a
 neural-specific promoter. The cortical and hippocampal brain regions of
 the transgenic mice display extracellular beta-amyloid immunoreactive
 deposits varying in size (<5-50 um) and abundance. These results
 suggest that one mechanism of beta-amyloid formation may involve a
 disruption of the normal ratio of neuronal beta -APP
 isoform expression and support a direct relationship between increased
 expression of Kunitz inhibitor-bearing beta -APP
 isoforms and beta-amyloid deposition.

ST amyloid A4 isoform imbalance brain Alzheimer
 IT Brain, composition
 (beta-amyloid deposition in, amyloid A4 isoform imbalance in, in
 Alzheimer's disease)

IT Mental disorder
 (Alzheimer's disease, amyloid A4 isoform imbalance in brain
 beta-amyloid deposition in)

IT Proteins, specific or class
 RL: BIOL (Biological study)
 (amyloid A4, brain deposits of, amyloid
 A4 isoform imbalance in, in Alzheimer's disease)

IT Glycoproteins, specific or class
 RL: BIOL (Biological study)
 (amyloid A4695, imbalance in amyloid A4751 and, in

brain β -amyloid deposition in Alzheimer's disease)

IT Proteins, specific or class
 RL: BIOL (Biological study)
 (amyloid A4751, imbalance in amyloid A4695 protein and, in brain
 β -amyloid deposition in Alzheimer's disease)

L34 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1991:427110 HCAPLUS
 DN 115:27110
 ED Entered STN: 27 Jul 1991
 TI Synthesis and characterization of the Kunitz protease-inhibitor domain of
 the β -amyloid precursor protein
 AU Schilling, James; Wang, Yu; Lau, Ken; Smith, Leanne; Cordell,
 Barbara
 CS California Biotechnol. Inc., Mountain View, CA, 94043, USA
 SO Gene (1991), 98(2), 225-30
 CODEN: GENED6; ISSN: 0378-1119
 DT Journal
 LA English
 CC 14-10 (Mammalian Pathological Biochemistry)
 AB To understand the pathol. process by which amyloid is deposited in
 Alzheimer's disease, it is important to characterize the proteolytic
 processing events of the β -amyloid precursor protein (**.beta**
.-APP) from which the amyloid-forming fragment is excised. A
 potentially important component in β -**APP**
 processing is the 57-amino acid (aa) Kunitz serine protease inhibitor
 (KPI) located within the extracellular domain of both the 751- and 770-aa
 isoforms of β -**APP**. The authors have synthesized
 DNA encoding the 57-aa KPI domain as a necessary step in identifying the
 role of the protease inhibitor in β -**APP**
 processing and amyloid formation. A bacterial secretion system directed
 by the alkaline phosphatase signal peptide of Escherichia coli linked to a
 synthetic gene encoding KPI was used to produce soluble, extracellular
 recombinant KPI (reKPI) protein. The reKPI protein was purified to
 homogeneity from bacterial supernatants and was biochem. and biol.
 characterized. Complete aa sequence anal. confirmed the fidelity of the
 reKPI, and fast-atom bombardment mass-spectral anal. was used to document
 that reKPI was of the predicted Mr. The reKPI is as active on a molar
 basis as the inhibitor-containing β -**APP** when assayed
 for inhibition of trypsin activity. Together these data suggest that
 reKPI protein is properly folded and lacking in modified aa. Hence, this
 reKPI will be an important reagent in gaining a better understanding of
 the role of the KPI domain in β -**APP** function and
 metabolism, as well as in the proteolytic events involved in β -amyloid
 formation.

ST Kunitz protease inhibitor amyloid precursor protein
 IT Protein sequences
 (for β -amyloid precursor protein Kunitz protease inhibitor domain,
 Alzheimer's disease pathogenesis in relation to)

IT Mental disorder
 (Alzheimer's disease, pathogenesis of, β -amyloid precursor protein
 processing in, formation and characterization of recombinant Kunitz
 protease-inhibitor domain of β -amyloid precursor protein in
 relation to)

IT Glycoproteins, specific or class
 RL: PRP (Properties)
 (amyloid A4, pre-, formation and
 characterization of recombinant Kunitz protease-inhibitor domain of,
 Alzheimer's disease pathogenesis in relation to)

IT 117312-67-1, 289-345-Glycoprotein (human clone λ APCP168i4 amyloid
 A4 precursor protein moiety reduced)
 RL: BIOL (Biological study)
 (recombinant, amino acid sequence of, Alzheimer's disease pathogenesis
 in relation to)

=> d all 143 tot

L43 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2004:176537 HCAPLUS
 DN 140:231420
 ED Entered STN: 04 Mar 2004
 TI Protein and cDNA sequences of a novel human β -
 secretase and use in screening drugs for treating Alzheimer's
 disease
 IN Gurney, Mark E.; Bienkowski, Michael J.; Heinrikson, Robert L.; Parodi,
 Luis A.; Yan, Riqiang
 PA Pharmacia & Upjohn Company, USA
 SO U.S., 103 pp., Cont.-in-part of U.S. Ser. No. 404,133, abandoned.
 CODEN: USXXAM
 DT Patent
 LA English
 IC ICM G01N033-53
 ICS C07K017-00; A61K038-00
 INCL 435007100; 530350000; 530300000
 CC 7-2 (Enzymes)
 Section cross-reference(s): 3, 14
 FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6699671	B1	20040302	US 1999-416901	19991013 <--
	WO 2000017369	A2	20000330	WO 1999-US20881	19990923 <--
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	IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD,				
	MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,				
	SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,				
	BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,				
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	CN 1502692	A	20040609	CN 2003-10119663	19990923 <--
	CN 1502696	A	20040609	CN 2003-10119664	19990923 <--
	US 6420534	B1	20020716	US 2000-548372	20000412 <--
	US 6440698	B1	20020827	US 2000-548367	20000412 <--
	US 2003104365	A1	20030605	US 2000-548366	20000412 <--
	US 6797487	B2	20040928		
	US 6706485	B1	20040316	US 2000-548376	20000412 <--
	US 6737510	B1	20040518	US 2000-548373	20000412 <--
	US 6825023	B1	20041130	US 2000-548368	20000412 <--
	US 6867018	B1	20050315	US 2000-548365	20000412 <--
	US 6500667	B1	20021231	US 2000-551853	20000418 <--
	CA 2397786	AA	20010405	CA 2000-2397786	20000922 <--
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	LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,				
	SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,				
	YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,				
	DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,				
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	AU 2000076071	A5	20010430	AU 2000-76071	20000922 <--
	AU 782312	B2	20050721		
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	GB 2357767	B2	20020821		
	GB 2367060	A1	20020327	GB 2001-25934	20000922 <--
	GB 2367060	B2	20030604		

EP 1224297	A2	20020724	EP 2000-965338	20000922 <--
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IE, SI, LT, LV, FI, RO, MK, CY, AL				
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NZ 517297	A	20040430	NZ 2000-517297	20000922 <--
US 6844148	B1	20050118	US 2000-668314	20000922 <--
US 2001016324	A1	20010823	US 2001-794927	20010227 <--
US 6727074	B2	20040427		
US 2001021391	A1	20010913	US 2001-794743	20010227 <--
US 6913918	B2	20050705		
US 2002037315	A1	20020328	US 2001-794748	20010227 <--
US 2002064819	A1	20020530	US 2001-794925	20010227 <--
US 6828117	B2	20041207		
US 2001018208	A1	20010830	US 2001-795847	20010228 <--
US 6753163	B2	20040622		
US 2002081634	A1	20020627	US 2001-681442	20010405 <--
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WO 2001050829	A2	20010719	WO 2001-IB799	20010509 <--
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US 2005080232	A1	20050414	US 2003-477076	20010509 <--
US 2004043408	A1	20040304	US 2003-652927	20030829 <--
US 2004048303	A1	20040311	US 2003-652830	20030829 <--
US 2004166507	A1	20040826	US 2003-652045	20030829 <--
US 2004234976	A1	20041125	US 2003-476935	20031106 <--
US 2005196398	A1	20050908	US 2004-817979	20040405 <--
PRAI US 1998-101594P	P	19980924	<--	
US 1999-155493P	P	19990923	<--	
US 1999-404133	B2	19990923	<--	
WO 1999-US20881	A2	19990923	<--	
CN 1999-811202	A	19990923	<--	
GB 2000-23315	A3	19990923	<--	
US 1999-416901	A3	19991013	<--	
US 1999-169232P	P	19991206	<--	
EP 2000-965338	A3	20000922	<--	
US 2000-668314	A1	20000922	<--	
WO 2000-US26080	W	20000922	<--	
WO 2001-IB798	W	20010509		
WO 2001-IB799	W	20010509		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
US 6699671	ICM	G01N033-53	
	ICS	C07K017-00; A61K038-00	
	INCL	435007100; 530350000; 530300000	
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
WO 2000017369	ECLA	C07K014/47A3; C12N009/64F2C23	<--
US 6420534	NCL	435/226.000; 435/023.000; 435/024.000; 435/069.100; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6440698	NCL	435/069.100; 435/252.300; 435/320.100; 435/325.000; 536/023.100	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2003104365	NCL	435/006.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6706485	NCL	435/007.100; 435/069.100; 435/183.000; 435/195.000; 435/212.000; 435/320.100; 530/300.000; 530/350.000;	

		536/023.100; 536/023.400; 536/023.500	
US 6737510	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
	NCL	530/350.000; 435/219.000	
US 6825023	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
	NCL	435/226.000; 435/183.000; 530/300.000; 530/324.000; 530/350.000	
US 6867018	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
	NCL	435/069.100; 435/252.300; 435/320.100; 435/325.000; 530/300.000; 530/350.000; 536/023.100	
US 6500667	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
	NCL	435/375.000; 514/044.000; 536/023.100; 536/024.100; 536/024.500	
WO 2001023533	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
GB 2357767	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
GB 2367060	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
EP 1249498	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6844148	NCL	435/004.000; 435/325.000; 530/350.000	
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US 2001016324	NCL	435/007.100	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2001021391	NCL	424/450.000	
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	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2002064819	NCL	435/069.100	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2001018208	NCL	435/325.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2002081634	NCL	435/007.210	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
WO 2001049097	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
WO 2001049098	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
WO 2001050829	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2005080232	NCL	530/350.000	
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US 2004043408	NCL	435/006.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2004048303	NCL	435/006.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
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	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2004234976	NCL	435/006.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2005196398	NCL	424/146.100; 435/006.000; 435/069.100; 435/226.000; 435/320.100; 435/325.000; 536/023.200	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
AB	The present invention provides protein and cDNA sequences of a novel human β -secretase. The present invention also provides the enzyme and enzymic procedures for cleaving the β secretase cleavage site of the APP protein. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease.		
ST	sequence human secretase screening drug Alzheimer disease		
IT	Protein motifs (DTG, DSG; protein and cDNA sequences of novel human β -secretase and use in screening drugs for treating Alzheimer's disease)		
IT	Alzheimer's disease Drug screening Human Molecular cloning Protein sequences cDNA sequences		

- (protein and cDNA sequences of novel human β -
secretase and use in screening drugs for treating Alzheimer's
disease)
- IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); RCT (Reactant);
BIOL (Biological study); RACT (Reactant or reagent)
(protein and cDNA sequences of novel human β -
secretase and use in screening drugs for treating Alzheimer's
disease)
- IT Amyloid
RL: BPN (Biosynthetic preparation); BIOL (Biological
study); PREP (Preparation)
(β -; protein and cDNA sequences of novel human β -
secretase and use in screening drugs for treating Alzheimer's
disease)
- IT 666867-40-9DP, β -Secretase (human),
subfragments are claimed
RL: BPN (Biosynthetic preparation); BSU (Biological study,
unclassified); PRP (Properties); BIOL (Biological study);
PREP (Preparation)
(amino acid sequence; protein and cDNA sequences of novel human
 β -secretase and use in screening drugs for
treating Alzheimer's disease)
- IT 666867-39-6, DNA (human β -secretase cDNA
plus flanks)
RL: BSU (Biological study, unclassified); PRP (Properties);
BIOL (Biological study)
(nucleotide sequence; protein and cDNA sequences of novel human
 β -secretase and use in screening drugs for
treating Alzheimer's disease)
- IT 158736-49-3P, Proteinase asp2
RL: BPN (Biosynthetic preparation); BSU (Biological study,
unclassified); PRP (Properties); BIOL (Biological study);
PREP (Preparation)
(protein and cDNA sequences of novel human β -
secretase and use in screening drugs for treating Alzheimer's
disease)
- IT 666869-29-0, 1: PN: US6699671 SEQID: 1 unclaimed DNA 666869-31-4, 3: PN:
US6699671 SEQID: 3 unclaimed DNA 666869-33-6, 7: PN: US6699671 SEQID: 7
unclaimed DNA 666869-35-8, 9: PN: US6699671 SEQID: 9 unclaimed DNA
666869-37-0 666869-39-2 666869-41-6 666869-43-8 666869-45-0
666869-47-2 666869-49-4 666869-51-8 666869-53-0 666869-55-2
666869-57-4 666869-59-6 666869-60-9 666869-61-0 666869-62-1
666869-63-2 666869-64-3 666869-65-4 666869-66-5 666869-67-6
666869-68-7 666869-69-8 666869-70-1 666869-71-2 666869-72-3
666869-73-4 666869-75-6 666869-77-8 666869-79-0 666869-81-4
666869-83-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; protein and cDNA sequences of a novel
human β -secretase and use in screening drugs
for treating Alzheimer's disease)
- IT 666869-30-3 666869-32-5 666869-34-7 666869-36-9 666869-38-1
666869-40-5 666869-42-7 666869-44-9 666869-46-1 666869-48-3
666869-50-7 666869-52-9 666869-54-1 666869-56-3 666869-58-5
666869-74-5 666869-76-7 666869-78-9 666869-80-3 666869-82-5
666869-84-7 666869-85-8
RL: PRP (Properties)
(unclaimed protein sequence; protein and cDNA sequences of a novel
human β -secretase and use in screening drugs
for treating Alzheimer's disease)
- IT 186142-28-9 252256-37-4 262364-47-6 262364-48-7
300584-89-8 302566-59-2 333322-60-4 348636-36-2 350241-65-5
350241-67-7 350241-69-9 350241-71-3
RL: PRP (Properties)
(unclaimed sequence; protein and cDNA sequences of a novel human
 β -secretase and use in screening drugs for

treating Alzheimer's disease)

RE.CNT 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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- (4) Anon; WO 9640885 1996 HCAPLUS
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- (13) Anon; WO 9964587 1999 HCAPLUS
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L43 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:473269 HCAPLUS

DN 139:47180

ED Entered STN: 20 Jun 2003

TI Treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compounds that decrease membrane depolarization or calcium influx caused by aggregated β -amyloid

IN Ingram, Vernon M.; Blanchard, Barbara J.; Stockwell, Brent R.

PA USA

SO U.S. Pat. Appl. Publ., 33 pp., Cont.-in-part of U.S. Ser. No. 706,574.

CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-4035

INCL 514417000

CC 1-11 (Pharmacology)

Section cross-reference(s): 14

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003114510	A1	20030619	US 2002-51663	20020118 <--
	US 6942963	B1	20050913	US 2000-706574	20001103 <--
	US 2003105152	A1	20030605	US 2002-143534	20020510 <--
	WO 2003068147	A2	20030821	WO 2003-US1672	20030121
	WO 2003068147	A3	20040318		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW			
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	EP 1474126	A2	20041110	EP 2003-707454	20030121
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
PRAI	US 2000-706574	A2	20001103 <--		
	US 1997-35847P	P	19970110 <--		
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	US 1998-5215	A2	19980109 <--		
	US 2002-51663	A2	20020118		
	US 2002-143534	A	20020510		
	WO 2003-US1672	W	20030121		

CLASS

PATENT NO. CLASS PATENT FAMILY CLASSIFICATION CODES

US 2003114510 ICM A61K031-4035
 INCL 514417000
 US 2003114510 NCL 514/417.000
 ECLA A61K031/00; A61K031/137; A61K031/138; A61K031/192;
 A61K031/225; A61K031/277; A61K031/40; A61K031/475;
 A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
 US 6942963 NCL 435/003.000; 435/808.000; 436/063.000; 436/164.000;
 436/172.000; 436/182.000; 436/800.000; 436/805.000
 ECLA A61K038/08; C07K001/04C; C07K007/06A; G01N033/68V2 <--
 US 2003105152 NCL 514/417.000
 ECLA A61K031/00; A61K031/137; A61K031/138; A61K031/192;
 A61K031/225; A61K031/277; A61K031/40; A61K031/475;
 A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
 WO 2003068147 ECLA A61K031/00; A61K031/137; A61K031/138; A61K031/192;
 A61K031/225; A61K031/277; A61K031/40; A61K031/4035;
 A61K031/475; A61K031/485; A61K031/55; G01N033/68V2

AB The invention involves identification of a mechanism of β -amyloid peptide cytotoxicity, which enables treatment of conditions caused by β -amyloid peptide aggregates by administration of compds. which antagonize the mechanism of cytotoxicity. The invention includes the identification and isolation of compds. which can reduce the neurotoxic effects of such aggregates. Methods for treating conditions resulting from neurotoxic β -amyloid peptide aggregates, such as Alzheimer's disease and pharmaceutical prepn.s. are provided. Also provided are methods for selecting addnl. compds. which can reduce the neurotoxic effects of β -amyloid aggregates. Specifically claimed is a method for treating Alzheimer's disease using a compound that decreases membrane depolarization of neuronal cells or decreases the calcium influx caused by aggregated β -amyloid ($A\beta$) protein degradation products,. The compds. used in treatment are tyrosine kinase inhibitors, chloride channel antagonists, dopamine receptor agonists, and $\alpha 2$ -adrenergic receptor antagonists. These compds. can be used in combination with β -amyloid vaccine.

ST beta amyloid aggregate neurotoxicity treatment membrane depolarization inhibitor; Alzheimers disease treatment membrane depolarization inhibitor; calcium influx inhibitor beta amyloid aggregate neurotoxicity treatment

IT Membrane potential
 (biol.; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Glutamate antagonists
 (mGluR1; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Fluorescent substances
 (potentiometric, for drug screening assay; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Chloride channel blockers
 (treatment composition containing; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Anti-Alzheimer's agents
 (treatment of; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)

IT Alzheimer's disease
 Biological transport
 Cell membrane
 Dopamine agonists
 Drug screening
 Human
 Nerve
 Nervous system agents
 Neurotoxicity
 (treatments for conditions caused by neurotoxic β -amyloid peptide

- aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT Peptides, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT Adrenoceptor antagonists
(α 2-, treatment composition containing; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT Amyloid
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(β -; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT Vaccines
(β -amyloid, along with agents inhibiting neuronal membrane depolarization; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT 70363-83-6, Bis(1,3-dibutylbarbituric acid) trimethine oxonol
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(as potentiometric agent for drug screening; treatment for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx caused by aggregated β -amyloid)
- IT 158736-49-3, β -Secretase 338454-52-7, γ -Secretase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(combined treatment with a secretase inhibitor; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT 79079-06-4, EGF receptor tyrosine kinase 80449-02-1, Tyrosine kinase 152787-58-1, TrkA receptor tyrosine kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, treatment composition containing; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; treatments for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx)
- IT 51-61-6, Dopamine, biological studies 55-10-7, Vanillyl-mandelic acid 131-03-3, Rauwolscine 911-45-5, Clomiphen 1845-11-0, Nafoxidine 71636-61-8, SKF81297 118409-60-2, Tyrphostin 47 145915-58-8, 4,5-Dianilinophthalimide 148741-30-4, Tyrphostin AG 879 150145-89-4 198419-91-9, LY367385
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment for conditions caused by neurotoxic β -amyloid peptide aggregates using compds. that decrease membrane depolarization or calcium influx caused by aggregated β -amyloid)
- IT 69-65-8, D-Mannitol 83-67-0, Theobromine 111-58-0, N-Oleoyl ethanolamine 130-61-0, Thioridazine Hydrochloride 302-27-2, Aconitine 312-84-5, D-Serine 569-57-3, Chlorotrianisene 646-25-3, 1,10-Diaminodecane 1847-63-8, Nafoxidine hydrochloride 2315-02-8, Oxymetazoline Hydrochloride 2792-66-7, α -Methyl-DL-aspartic acid

3724-89-8 5302-45-4 6211-32-1, Rauwolschine hydrochloride 6620-60-6,
 Proglumide 9087-70-1, Aprotinin 13311-84-7, Flutamide 13434-13-4,
 Actinonin 24280-93-1, Mycophenolic acid 33507-63-0, Substance P
 (peptide) 34183-22-7, Propafenone Hydrochloride 37686-84-3
 39740-82-4 42200-33-9, Nadolol 54965-24-1, Tamoxifen citrate
 66104-23-2, Pergolide methanesulfonate 73590-58-6, Omeprazole
 76824-35-6, Famotidine 78739-01-2, D-(-)-2-Amino-4-Phosphonobutyric acid
 97752-20-0 130506-22-8, 6-Nitroso-1,2-benzopyrone

RL: PAC (Pharmacological activity); THU (Therapeutic
 use); BIOL (Biological study); USES (Uses)

(treatments for conditions caused by neurotoxic β -amyloid peptide
 aggregates using compds. that decrease membrane depolarization or
 calcium influx)

IT 543805-01-2 543805-02-3

RL: PRP (Properties)

(unclaimed protein sequence; treatments for conditions caused by
 neurotoxic β -amyloid peptide aggregates using compds. that
 decrease membrane depolarization or calcium influx caused by aggregated
 β -amyloid)

IT 131602-53-4

RL: PRP (Properties)

(unclaimed sequence; treatments for conditions caused by neurotoxic
 β -amyloid peptide aggregates using compds. that decrease membrane
 depolarization or calcium influx caused by aggregated β -amyloid)

L43 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:435317 HCAPLUS

DN 139:30831

ED Entered STN: 06 Jun 2003

TI Treatments for neurotoxicity in Alzheimer's disease

IN Ingram, Vernon M.; Blanchard, Barbara J.; Stockwell, Brent R.

PA USA

SO U.S. Pat. Appl. Publ., 34 pp., Cont.-in-part of U.S. Ser. No. 51,663.

CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-4035

ICS C12Q001-00

INCL 514417000; 435004000

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003105152	A1	20030605	US 2002-143534	20020510 <--
	US 6942963	B1	20050913	US 2000-706574	20001103 <--
	US 2003114510	A1	20030619	US 2002-51663	20020118 <--
	WO 2003068147	A2	20030821	WO 2003-US1672	20030121
	WO 2003068147	A3	20040318		
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	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	EP 1474126	A2	20041110	EP 2003-707454	20030121
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
PRAI	US 2000-706574	A2	20001103 <--		
	US 2002-51663	A2	20020118		
	US 1997-35847P	P	19970110 <--		
	US 1997-960188	B1	19971029 <--		

US 1998-5215 A2 19980109 <--
 US 2002-143534 A 20020510
 WO 2003-US1672 W 20030121

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 2003105152	ICM	A61K031-4035
	ICS	C12Q001-00
	INCL	514417000; 435004000
US 2003105152	NCL	514/417.000
	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/475; A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
US 6942963	NCL	435/003.000; 435/808.000; 436/063.000; 436/164.000; 436/172.000; 436/182.000; 436/800.000; 436/805.000
	ECLA	A61K038/08; C07K001/04C; C07K007/06A; G01N033/68V2 <--
US 2003114510	NCL	514/417.000
	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/475; A61K031/485; A61K031/55; G01N033/50D2; G01N033/68V2 <--
WO 2003068147	ECLA	A61K031/00; A61K031/137; A61K031/138; A61K031/192; A61K031/225; A61K031/277; A61K031/40; A61K031/4035; A61K031/475; A61K031/485; A61K031/55; G01N033/68V2

AB The invention involves identification of a mechanism of β -amyloid peptide cytotoxicity, which enables treatment of conditions caused by β -amyloid peptide aggregates by administration of compds. which antagonize the mechanism of cytotoxicity. The invention includes the identification and isolation of compds. which can reduce the neurotoxic effects of such aggregates. Methods for treating conditions resulting from neurotoxic β -amyloid peptide aggregates, such as Alzheimer's disease and pharmaceutical prepn. are provided. Also provided are methods for selecting addnl. compds. which can reduce the neurotoxic effects of β -amyloid aggregates. A β 1-42 aggregates increased neuronal cell depolarization in rat PC12 and human NT neuronal cells. A random library of 1540 biol. active compds. was screened against undifferentiated PC12 cells pretreated with A β 1-42 peptide. The most effective elimination of depolarization was achieved with two tyrosine kinase inhibitors, DAPH1 (4,5-dianilinophthalimide, EGF-receptor specific) and Tyrphostin AG879 (TrkA specific), and also nafoxidine (antiestrogen receptor, chloride channel antagonist). These were active in low micromolar concentration

ST neurotoxicity beta amyloid Alzheimer disease treatment; neuron membrane depolarization beta amyloid aggregate; tyrosine kinase inhibitor Alzheimer treatment; nafoxidine Alzheimer treatment neuron membrane stabilization

IT Vaccines
 (A β , along with agents inhibiting neuronal membrane depolarization; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Animal cell line
 (PC12; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Membrane potential
 (biol.; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Cell membrane
 (compds. decreasing β -amyloid aggregate-caused depolarization of neuronal cell; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT Drug screening
 Human
 Nerve
 Neurotoxicity
 (compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)

IT High throughput screening
 (drug; compns. and methods for treatment of β -amyloid aggregate

- neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Drug screening**
(high throughput; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Glutamate antagonists**
(mGluR1, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Glutamate receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(metabotropic, mGluR1, antagonists, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Nerve**
(neuron; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Fluorescent substances**
(potentiometric; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Chemical compounds**
(screening of small; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Combinatorial library**
(screening of; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Peptides, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(screening of; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Chloride channel blockers**
- Dopamine agonists**
(treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Alzheimer's disease**
(treatment of; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Adrenoceptor antagonists**
(α 2-, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT **Amyloid**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(β -; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 911-45-5, Clomiphen 1845-11-0, Nafoxidine
RL: BSU (Biological study, unclassified); CST (Combinatorial study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); USES (Uses)
(as chloride channel antagonist, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 55-10-7, Vanillyl-mandelic acid 71636-61-8, SKF81297
RL: BSU (Biological study, unclassified); CST (Combinatorial study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); USES (Uses)
(as dopamine receptor agonist, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in

- Alzheimer's disease and for drug screening)
- IT 51-61-6, Dopamine, biological studies
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as dopamine receptor agonist, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 150145-89-4 168560-79-0, AIDA 198419-91-9, LY367385
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as mGluR1 antagonist, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 70363-83-6, Bis(1,3-dibutylbarbituric acid) trimethine oxonol
 RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
 (as potentiometric agent for drug screening; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 446-72-0, Genistein 70563-58-5, Herbimycin A 71897-07-9, Tyrphostin AG 1295 125697-92-9, Lavendustin A 153436-53-4, Tyrphostin AG 1478
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (as tyrosine kinase inhibitor inactive in assay for reduction of membrane depolarization; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 145915-58-8, 4,5-Dianilinophthalimide
 RL: BSU (Biological study, unclassified); CST (Combinatorial study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); USES (Uses)
 (as tyrosine kinase inhibitor, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 118409-60-2, Tyrphostin 47 148741-30-4, Tyrphostin AG 879
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as tyrosine kinase inhibitor, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 131-03-3, Rauwolscine
 RL: BSU (Biological study, unclassified); CST (Combinatorial study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); USES (Uses)
 (as α 2-adrenergic receptor antagonist, treatment composition containing; compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 338454-52-7, γ -Secretase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (compns. and methods for treatment of β -amyloid aggregate neurotoxicity in Alzheimer's disease and for drug screening)
- IT 69-65-8, D-Mannitol 83-67-0, Theobromine 111-58-0, N-Oleoyl ethanolamine 130-61-0, Thioridazine Hydrochloride 302-27-2, Aconitine 312-84-5, D-Serine 569-57-3, Chlorotrianisene 646-25-3, 1,10-Diaminodecane 1847-63-8, Nafoxidine hydrochloride 2315-02-8, Oxymetazoline Hydrochloride 2792-66-7, α -Methyl-DL-aspartic acid 3724-89-8 5302-45-4 6211-32-1, Rauwolscine hydrochloride 6620-60-6, Proglumide 9087-70-1, Aprotinin 13311-84-7, Flutamide 13434-13-4, Actinonin 24280-93-1, Mycophenolic acid 34183-22-7, Propafenone Hydrochloride 37686-84-3 39740-82-4 42200-33-9, Nadolol

54965-24-1, Tamoxifen citrate 66104-23-2, Pergolide methanesulfonate
 73590-58-6, Omeprazole 76824-35-6, Famotidine 78739-01-2,
 D-(-)-2-Amino-4-Phosphonobutyric acid 97752-20-0 130506-22-8,
 6-Nitroso-1,2-benzopyrone

RL: BSU (Biological study, unclassified); CST (Combinatorial
 study, unclassified); PAC (Pharmacological activity); THU
 (Therapeutic use); BIOL (Biological study); CMBI
 (Combinatorial study); USES (Uses)

(compsns. and methods for treatment of β -amyloid aggregate
 neurotoxicity in Alzheimer's disease and for drug screening)

IT 33507-63-0, Substance P (peptide)

RL: BSU (Biological study, unclassified); PAC
 (Pharmacological activity); THU (Therapeutic use);
 BIOL (Biological study); USES (Uses)

(compsns. and methods for treatment of β -amyloid aggregate
 neurotoxicity in Alzheimer's disease and for drug screening)

IT 7440-70-2, Calcium, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological
 study)

(decreasing aggregated β -amyloid-caused neuronal cell influx of;
 compsns. and methods for treatment of β -amyloid aggregate
 neurotoxicity in Alzheimer's disease and for drug screening)

IT 158736-49-3, β -Secretase

RL: BSU (Biological study, unclassified); BIOL (Biological
 study)

(inhibitor, treatment composition containing; compsns. and methods for treatment
 of β -amyloid aggregate neurotoxicity in Alzheimer's disease and
 for drug screening)

IT 79079-06-4, EGF receptor tyrosine kinase 80449-02-1, Tyrosine kinase
 152787-58-1, TrkA receptor tyrosine kinase

RL: BSU (Biological study, unclassified); BIOL (Biological
 study)

(inhibitors, treatment composition containing; compsns. and methods for treatment
 of β -amyloid aggregate neurotoxicity in Alzheimer's disease and
 for drug screening)

IT 539902-04-0 539902-05-1

RL: PRP (Properties)

(unclaimed protein sequence; treatments for neurotoxicity in
 Alzheimer's disease)

IT 131602-53-4

RL: PRP (Properties)

(unclaimed sequence; treatments for neurotoxicity in Alzheimer's
 disease)

L43 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:615647 HCAPLUS

DN 137:150257

ED Entered STN: 16 Aug 2002

TI Method of treating amyloid β precursor protein disorder

IN Friedhoff, Lawrence; Buxbaum, Joseph; Cullen, Edward I.

PA Andrx Corporation, USA

SO PCT Int. Appl., 70 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07K

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002062824	A2	20020815	WO 2002-US3256	20020205
	WO 2002062824	A3	20021121		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,			

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT,
 RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US,
 UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002107173 A1 20020808 US 2002-67593 20020205 <--
 CA 2437480 AA 20020815 CA 2002-2437480 20020205
 EP 1366061 A2 20031203 EP 2002-718903 20020205
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 US 2005215621 A1 20050929 US 2005-72863 20050304 <--
 PRAI US 2001-265886P P 20010205
 US 1999-163608P P 19991104 <--
 US 2000-219435P P 20000720 <--
 US 2000-223987P P 20000809 <--
 US 2002-67593 A1 20020205
 WO 2002-US3256 W 20020205

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002062824	ICM	C07K
WO 2002062824	ECLA	A61K031/00; A61K031/192; A61K031/22; A61K031/366; A61K031/40; A61K031/401; G01N033/68V2
US 2002107173	NCL	514/001.000
	ECLA	A61K031/00; A61K031/192; A61K031/22; A61K031/366; A61K031/40; A61K031/401; G01N033/68V2 <--
CA 2437480	ECLA	A61K031/00; A61K031/192; A61K031/22; A61K031/366; A61K031/40; A61K031/401; G01N033/68V2
EP 1366061	ECLA	A61K031/00; A61K031/192; A61K031/22; A61K031/366; A61K031/40; A61K031/401; G01N033/68V2
US 2005215621	NCL	514/423.000; 514/460.000; 514/548.000; 435/007.100; 435/007.920
	ECLA	A61K031/00; A61K031/192; A61K031/22; A61K031/366; A61K031/40; A61K031/401; G01N033/68V2 <--

AB Methods for the treatment and prevention of APP processing disorders such as Alzheimer's disease and Down's Syndrome which are based on the administration of an effective amount of a HMG-CoA reductase inhibitor to a mammal are disclosed. Addnl., methods for the treatment and prevention of APP processing disorders such as Alzheimer's disease and Down's Syndrome which are based on the reduction of cellular cholesterol in a mammal are disclosed. These methods reduce the amount of A β peptides or decrease the formation of A β peptides or increase the clearance of A β peptides in a mammal suffering from Alzheimer's disease and Down's Syndrome.

ST amyloid precursor protein disorder HMG CoA reductase inhibitor

IT Immunoassay

(agglutination test; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)

IT Bioassay

(complement fixation assay; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)

IT Immunoassay

(enzyme-linked immunosorbent assay; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)

IT Immunoassay

(fluorescence; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)

IT Immunoassay

(immunoblotting; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to

- determination of β -amyloid peptides in body fluids)
- IT Immunoassay
(immunodiffusion, gel diffusion; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Immunoassay
Immunoassay
(immunodiffusion; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Immunoassay
(immunoelectrophoresis; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Immunoassay
(immunoradiometric assay; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Buffers
(in β -amyloid peptide assays; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Alzheimer's disease
Anti-Alzheimer's agents
Down's syndrome
Drug delivery systems
Drug screening
Human
Hypolipemic agents
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT Amyloid precursor proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT Antibodies and Immunoglobulins
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(monoclonal, to β -amyloid peptides, capture and detection; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Anti-inflammatory agents
(nonsteroidal; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT Drug delivery systems
(oral, controlled-release; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT Antibodies and Immunoglobulins
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(precipitins, to β -amyloid peptides, immunoassay with; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)

- IT Immunoassay
(protein A; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Immunoassay
(radioimmunoassay; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Immunoassay
(sandwich; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Antibodies and Immunoglobulins
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(to β -amyloid peptides, capture and detection; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Amyloid
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study)
(β -, lowering of; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT Blood plasma
Blood serum
Brain
Cerebrospinal fluid
(β -amyloid peptides decrease in; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT Blood analysis
Body fluid
(β -amyloid peptides determination in; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to determination of β -amyloid peptides in body fluids)
- IT 9028-35-7, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HMG-CoA reductase, inhibitors; method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT 75225-51-3, Lovastatin acid
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT 75330-75-5, Lovastatin
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of treating amyloid precursor protein disorders using HMG-CoA reductase inhibitors and other agents in relation to decrease of cellular cholesterol and determination of β -amyloid peptides in body fluids)
- IT 73573-88-3, Mevastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin

93957-54-1, Fluvastatin 134523-00-5, Atorvastatin 143201-11-0,
Rivastatin

RL: PAC (Pharmacological activity); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)

(method of treating amyloid precursor protein disorders using HMG-CoA
reductase inhibitors and other agents in relation to decrease of
cellular cholesterol and determination of β -amyloid peptides in body
fluids)

IT 158736-49-3, β -Secretase 338454-52-7,
 γ -Secretase 338455-07-5, α -Secretase

RL: BSU (Biological study, unclassified); BIOL (Biological
study)

(modifiers; method of treating amyloid precursor protein disorders
using HMG-CoA reductase inhibitors and other agents in relation to
decrease of cellular cholesterol and determination of β -amyloid peptides
in body fluids)

L43 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:518834 HCAPLUS

DN 137:59522

ED Entered STN: 12 Jul 2002

TI Crystal structure of beta-site APP-cleaving enzyme (BACE) and uses thereof

IN Choppa, Rajiv; Svenson, Kristine; Annis, Bethany; Akopian, Tatos N.; Bard,
Jonathan; Stahl, Mark Lloyd; Somers, William S.

PA American Home Products Corporation, USA

SO PCT Int. Appl., 88 pp.

CODEN: PIXXD2

DT Patent

LA English

IC G01N033-483

CC 7-5 (Enzymes)

Section cross-reference(s): 1, 63

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002025276	A1	20020328	WO 2001-US29387	20010919 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002055459	A1	20020509	US 2001-955737	20010919 <--
PRAI US 2000-234576P	P	20000922	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002025276	IC	G01N033-483
WO 2002025276	ECLA	C07K014/47A3; C12N009/64F <--
US 2002055459	NCL	514/001.000
	ECLA	C07K014/47A3; C12N009/64F <--

AB This invention is directed to the three dimensional crystal structure of
Beta-site APP Cleaving Enzyme (BACE), and to the use of this structure in
rational drug design methods to identify agents that may interact with
active sites of BACE. Such agents may represent new therapeutics in the
treatment and/or prevention of Alzheimer's Disease. The amino acid
sequence of the aspartic proteinase BACE is recorded in SwissProt
accession number P56817. BACE is the β -secretase
that cleaves β -amyloid precursor protein (APP) at residue 671. An
APP-inhibitor peptide has the sequence SER-GLU-VAL-ASN-Sta-VAL-ALA-GLU-
PHE, where Sta is the rare amino acid S-statine.

ST beta secretase BACE crystal structure drug screening

Alzheimer

IT Amyloid precursor proteins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (cleavage of; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT Alzheimer's disease
 Anti-Alzheimer's agents
 Crystal structure
 Drug screening
 Human
 Molecular cloning
 Molecular structure
 X-ray diffractometry
 (crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT Crystallography
 (x-ray; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT 439546-25-5, β -secretase (human gene BACE)
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (amino acid sequence; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT 158736-49-3, β -Site APP cleaving enzyme
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT 439085-08-2
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT 392103-88-7, GenBank AF190725
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (nucleotide sequence; crystal structure of beta-site APP-cleaving enzyme (BACE) in rational drug design of anti-Alzheimer's disease agents)

IT 439549-44-7 439549-87-8
 RL: PRP (Properties)
 (unclaimed sequence; crystal structure of beta-site APP-cleaving enzyme (BACE) and uses thereof)

RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD

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- (2) Hong, L; Science 2000, V290(5489), P150 HCAPLUS
- (3) Hynes; Biochemistry 1990, V29, P10018 HCAPLUS
- (4) Kohno; Biochemistry 1996, V35, P16094 HCAPLUS
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- (7) Sauder, M; J Mol Biol 2000, V300(2), P241
- (8) Scheidig; The Protein Society 1997, V6, P1806 HCAPLUS
- (9) Vassar; Science 1999, V286, P735 HCAPLUS
- (10) Zhang, Z; The EMBO Journal 1997, V16(20), P6141 HCAPLUS

L43 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:107514 HCAPLUS

DN 136:163293

ED Entered STN: 10 Feb 2002

TI BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or

treatment of neurodegenerative disorders
 IN Seidah, Nabil G.; Chretien, Michel; Cromlish, James A.
 PA Institut De Recherche Cliniques De Montreal (IRCM), Can.
 SO PCT Int. Appl., 64 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C12N009-00
 CC 7-2 (Enzymes)

Section cross-reference(s): 1, 13, 14

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2002010354	A2	20020207	WO 2001-CA1118	20010801 <--	
	W:			AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
	RW:			GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG		
	CA 2313828	AA	20020201	CA 2000-2313828	20000801 <--	
	CA 2417873	AA	20020207	CA 2001-2417873	20010801 <--	
	US 2004180417	A1	20040916	US 2004-343389	20040405 <--	
PRAI	CA 2000-2313828	A	20000801	<--		
	WO 2001-CA1118	W	20010801			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2002010354	ICM	C12N009-00	
WO 2002010354	ECLA	C07K014/47A3; C12N009/64F	<--
CA 2313828	ECLA	C07K014/47A3; C12N009/64F	<--
CA 2417873	ECLA	C07K014/47A3; C12N009/64F	<--
US 2004180417	NCL	435/184.000	
	ECLA	C07K014/47A3; C12N009/64F	<--

AB The present invention relates to β -secretase referred to as the beta-site APP-cleaving enzyme (BACE, Asp2, memapsin 2). More specifically, the present invention concerns a novel Asp-ase that processes BACE, referred to as BACE secretase/sheddase, and the use of this enzyme in the diagnosis, prevention or treatment of neurodegenerative disorders, such as Alzheimer's Disease. The present invention further comprises the use of BACE secretase/sheddase in a screening assay for the identification of agents capable of modifying its activity (modulating agents) as well as the use of BACE secretase/sheddase in a kit. A novel Asp-ase activity, referred to as BACE secretase/sheddase, has been found to cleave the ectodomain of BACE after Asp379 (SQDD↓) and Asp407 (VVFD↓), and likely after Asp451 (PQTD↓). The cleavage of BACE by BACE secretase/sheddase renders BACE soluble which in turns appears to enhance the generation of the amyloidogenic peptide A β , which has been implicated as a major factor in the etiol. of Alzheimer's Disease. Since truncation of BACE leads to increased A β production, BACE secretase/sheddase is an attractive target to modulate for medicinal and research purposes.

ST BACE secretase/sheddase Asp ase neurodegenerative disorder diagnosis therapy

IT Alzheimer's disease

Drug screening

High throughput screening

Susceptibility (genetic)

Test kits

(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Antibodies and Immunoglobulins

Antisense oligonucleotides

Ribozymes

RL: THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Cerebrospinal fluid

Platelet (blood)

(anal. of, for diagnosis; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Nervous system, disease

(degeneration; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Peptides, biological studies

RL: THU (Therapeutic use); BIOL (Biological study);

USES (Uses)

(inhibitor; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Diagnosis

(mol.; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Amyloid precursor proteins

RL: ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL

(Biological study); USES (Uses)

(use in screening; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT Amyloid

RL: ANT (Analyte); ARU (Analytical role, unclassified); BUU (Biological use, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(β -, anal. of the level of, for diagnosis; BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT 396078-28-7, BACE secretase/sheddase

RL: ARU (Analytical role, unclassified); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);

USES (Uses)

(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT 158736-49-3, β -Site APP-cleaving enzyme

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(BACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT 397251-28-4

RL: PRP (Properties)

(Unclaimed; bACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

IT 98849-88-8 141074-86-4 182916-29-6 252256-47-6 395183-00-3
 395183-01-4 395183-02-5 395183-03-6 397251-18-2 397251-19-3
 397251-20-6 397251-21-7 397251-22-8 397251-23-9 397251-24-0
 397251-25-1 397251-26-2 397251-27-3 397251-29-5

RL: PRP (Properties)

(unclaimed sequence; bACE secretase/sheddase, a novel Asp-ase that processes BACE (beta-site APP-cleaving enzyme), and use in drug screening, diagnosis, prevention, or treatment of neurodegenerative disorders)

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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L43 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2002:10812 HCAPLUS

DN 136:79718

ED Entered STN: 04 Jan 2002

TI Rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening

IN Bamdad, Cynthia C.; Bamdad, R. Shoshana

PA Minerva Biotechnologies Corporation, USA

SO PCT Int. Appl., 139 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM G01N033-68

CC 1-1 (Pharmacology)

Section cross-reference(s): 14

FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002001230	A2	20020103	WO 2001-US20232	20010625 <--
	WO 2002001230	A3	20030814		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	CA 2413884	AA	20020103	CA 2001-2413884	20010625 <--
	AU 2001070157	A5	20020108	AU 2001-70157	20010625 <--
	EP 1356296	A2	20031029	EP 2001-948711	20010625 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR			
	JP 2004526124	T2	20040826	JP 2002-506112	20010625 <--
PRAI	US 2000-602689	A	20000623	<--	
	US 2000-631818	A	20000803	<--	
	WO 2001-US20232	W	20010625		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002001230	ICM	G01N033-68
WO 2002001230	ECLA	G01N033/543M; G01N033/68V2 <--

JP 2004526124 FTERM 2G045/AA25; 2G045/CA25; 2G045/CA26; 2G045/CA30;
 2G045/CB17; 2G045/CB30; 2G045/DA36; 2G045/FA11;
 2G045/FA34; 2G045/FB11; 2G045/JA01; 2G054/AA06;
 2G054/AA07; 2G054/AA08; 2G054/AA10; 2G054/AB02;
 2G054/AB05; 2G054/CA21; 2G054/CA22; 2G054/CA23;
 2G054/EA03; 2G054/EA06; 2G054/FB01; 2G054/GA03;
 2G054/GA04; 2G054/GE01; 2G059/AA01; 2G059/BB12;
 2G059/BB14; 2G059/DD03; 2G059/DD13; 2G059/EE01;
 2G059/EE02; 2G059/EE07; 2G059/EE12; 2G059/EE13;
 2G059/FF03; 2G059/HH02; 2G059/KK04; 2G059/KK06;
 2G059/KK07; 4B063/QA05; 4B063/QA20; 4B063/QQ79;
 4B063/QQ91; 4B063/QR16; 4B063/QR55; 4B063/QR58;
 4B063/QR82; 4B063/QS12; 4B063/QS22; 4B063/QS32;
 4B063/QX01 <--

AB Methods, assays, and components are described in which biol. samples can be rapidly and sensitively analyzed for the presence of species associated with neurodegenerative disease. Techniques and components are provided for diagnosis of disease, as well as for screening of candidate drugs for treatment of neurodegenerative disease. The techniques are simple, extremely sensitive, and utilize readily-available components. Binding species, capable of binding a neurodegenerative disease aggregate-forming or aggregate-forming species, are fastened to surfaces of electrodes and surfaces of particles, or provided free in solution, to bind aggregate-forming species and/or be involved in aggregation.

ST aberrant protein fibril aggregation colloid; drug screening neurodegenerative disease kit

IT Brain, disease
 Prion diseases
 (Creutzfeldt-Jakob; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
 RL: DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
 (PrPSc; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Voltammetry
 (a.c.; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Spheres
 (beads; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
 RL: DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
 (bovine spongiform encephalopathy; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Proteins
 RL: DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
 (complexes; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Nervous system, disease
 (degeneration; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Self-assembled monolayers
 (electroactive; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Immunoassay
 (enzyme-linked immunosorbent assay; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Enzymes, biological studies

RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
 (inhibitors, capsase; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Carboxyl group
 (ionized; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Aggregation
 Alzheimer's disease
 Animal
 Animal cell
 Blood analysis
 Cerebrospinal fluid
 Colloids
 Diagnosis
 Drug screening
 Feed
 Fibril
 High throughput screening
 Human
 Immobilization, molecular or cellular
 Livestock
 Magnetic particles
 Microtiter plates
 Milk
 Molecular association
 Molecular recognition
 Parkinson's disease
 Protein sequences
 Test kits
 Transplant and Transplantation
 UV and visible spectroscopy
 (rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Enzymes, biological studies
 RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT p53 (protein)
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Metalloenes
 RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT DNA
 RL: DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Peptides, biological studies
 RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Nucleic acids
 Oligonucleotides
 Proteins
 RL: PRP (Properties)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation

- in neurodegenerative disease diagnosis and drug screening)
- IT Antibodies and Immunoglobulins
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT Brain, disease
(spongiform encephalopathy, transmissible; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT Sensors
(surface plasmon resonance chip; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT Transferrins
RL: BSU (Biological study, unclassified); CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); BIOL (Biological study); PROC (Process)
(τ -transferrins; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT Amyloid
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(β -, C-terminal fragment; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT Amyloid
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(β -; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT 167396-02-3 286411-43-6 286411-44-7 286411-46-9 286411-47-0
286411-48-1
RL: PRP (Properties)
(Unclaimed; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT 7732-18-5, Water, biological studies
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT 58-85-5, 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)- 70-18-8, Glycine, L- γ -glutamyl-L-cysteinyl-, properties 102-54-5, Ferrocene 139-13-9, Glycine, N,N-bis(carboxymethyl)- 573-58-0, 1-Naphthalenesulfonic acid, 3,3'-[[1,1'-biphenyl]-4,4'-diylbis(azo)]bis(4-amino-, disodium salt 2390-54-7, Benzothiazolium, 2-[4-(dimethylamino)phenyl]-3,6-dimethyl-, chloride 6066-82-6, 2,5-Pyrrolidinedione, 1-hydroxy- 9001-78-9, Phosphatase, alkaline 9013-20-1, Streptavidin 10487-90-8, Phenol, 2,2'-[(6,6'-dimethyl[1,1'-biphenyl]-2,2'-diyl)bis(nitrilomethylidyne)]bis- 64691-70-9, Pyridine, 2,2'-[1,2-ethanediylbis(thio-2,1-ethanediyl)]bis-
RL: CPS (Chemical process); PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT 7440-57-5, Gold, properties
RL: DEV (Device component use); PRP (Properties); USES (Uses)
(rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)
- IT 78990-62-2, Calpain 158736-49-3, β -Secretase 338454-52-7, γ -Secretase
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)

(rapid and sensitive detection of aberrant protein(fibril) aggregation
in neurodegenerative disease diagnosis and drug screening)

L43 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:780679 HCAPLUS
DN 135:327362
ED Entered STN: 26 Oct 2001
TI Nonsteroidal antiinflammatory drug (NSAID) and NSAID derivative amyloid
A β 42 polypeptide-lowering agents for the treatment of Alzheimer's
disease, and screening methods
IN Koo, Edward Hao Mang; Golde, Todd Eliot; Galasko, Douglas Roger
PA Mayo Foundation for Medical Education and Research, USA
SO PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-40
ICS A61K031-24; A61K031-195; A61K031-165
CC 1-11 (Pharmacology)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001078721	A1	20011025	WO 2001-US11956	20010412 <--
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2406383	AA	20011025	CA 2001-2406383	20010412 <--
	AU 2001057022	A5	20011030	AU 2001-57022	20010412 <--
	EP 1284729	A1	20030226	EP 2001-930491	20010412 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	JP 2003530437	T2	20031014	JP 2001-576021	20010412 <--
	US 2002128319	A1	20020912	US 2001-12606	20011207 <--
	US 6911466	B2	20050628		
	US 2005089945	A1	20050428	US 2004-928925	20040827 <--
	US 2005186559	A1	20050825	US 2005-113789	20050425 <--
PRAI	US 2000-196617P	P	20000413	<--	
	WO 2001-US11956	W	20010412		
	US 2001-12606	A3	20011207		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001078721	ICM	A61K031-40
	ICS	A61K031-24; A61K031-195; A61K031-165
WO 2001078721	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2
CA 2406383	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2
AU 2001057022	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2
EP 1284729	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2
US 2002128319	NCL	514/569.000
	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2
US 2005089945	NCL	435/023.000
	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24; A61K031/40; G01N033/68V2
US 2005186559	NCL	435/004.000; 435/006.000; 436/086.000
	ECLA	A61K031/165; A61K031/192; A61K031/195; A61K031/24;

A61K031/40; G01N033/68V2

<--

- AB A method is provided for preventing, delaying, or reversing the progression of Alzheimer's disease by administering an A β 42-lowering agent to a mammal under conditions in which levels of A β 42 are selectively reduced, levels of A β 38 are increased, and levels of A β 40 are unchanged. The invention provides methods and materials for developing and identifying A β 42-lowering agents. In addition, the invention provides methods for identifying agents that increase the risk of developing, or hasten progression of, Alzheimer's disease. The invention also provides compns. of A β 42-lowering agents and antioxidants, A β 42 lowering agents and non-selective secretase inhibitors, and A β 42 lowering agents and acetylcholinesterase inhibitors. The invention further provides kits containing A β 42-lowering agents, antioxidants, non-selective secretase inhibitors, and/or acetylcholinesterase inhibitors as well as instructions related to dose regimens for A β 42-lowering agents, antioxidants, non-selective secretase inhibitors, and acetylcholinesterase inhibitors. The agents of the invention include nonsteroidal antiinflammatory drugs (NSAIDs) and NSAID derivs.
- ST amyloid Abeta42 lowering agent Alzheimer drug; NSAID amyloid Abeta42 lowering agent Alzheimer drug; screening amyloid Abeta42 lowering agent Alzheimer drug
- IT Alzheimer's disease
 Anti-Alzheimer's agents
 Drug design
 Drug screening
 Ginkgo biloba
 (NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Enzymes, biological studies
 RL: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); BIOL (Biological study)
 (NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amino acids, biological studies
 RL: BAC (Biological activity or effector, except adverse);
 BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid precursor proteins
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Metabolism
 (catabolic; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Animal cell
 (mammalian; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Anti-inflammatory agents
 (nonsteroidal, and derivs.; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Antioxidants
 (pharmaceutical; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Transgene
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (transgenic animal; NSAID and NSAID derivative amyloid A β 42

- polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 34; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 36; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 37; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 38; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 39; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 40; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β -, A β 42; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT 50-78-2, Aspirin 80-08-0, Dapsone 489-84-9, Guaiazulene 501-36-0, Resveratrol 642-72-8, Benzydamine 4394-00-7, Niflumic acid 13710-19-5, Tolfenamic acid 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22494-42-4, Diflunisal 27470-51-5, Suxibuzone 31842-01-0, Indoprofen 34552-84-6, Isoxicam 36322-90-4, Piroxicam 36330-85-5, Fenbufen 40828-46-4, Suprofen 41340-25-4, Etodolac 42924-53-8, Nabumetone 51803-78-2, Nimesulide 53164-05-9, Acemetacin 59804-37-4, Tenoxicam 59973-80-7, Sulindac sulfone 71125-38-7, Meloxicam 74103-06-3, Ketorolac 123653-11-2, NS-398 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 188817-13-2, SC560 209125-28-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)
- IT 50-81-7, Vitamin C, biological studies 53-86-1, Indomethacin 53-86-1D, Indomethacin, derivs. 61-68-7, Mefenamic acid 64-19-7D, Acetic acid, aryl derivs., biological studies 79-09-4D, Propionic acid, aryl derivs. 458-37-7, Curcumin 530-78-9, Flufenamic acid 530-78-9D, Flufenamic acid, derivs. 644-62-2, Meclofenamic acid 644-62-2D, Meclofenamic acid, derivs. 1406-18-4, Vitamin E 1601-18-9 2878-86-6 5104-49-4,

Flurbiprofen 5104-49-4D, Flurbiprofen, derivs. 6264-33-1 15687-27-1,
 Ibuprofen 15687-27-1D, Ibuprofen, derivs. 22071-15-4D, Ketoprofen,
 derivs. 29679-58-1, Fenoprofen 29679-58-1D, Fenoprofen, derivs.
 49627-27-2, Sulindac sulfide 49627-27-2D, Sulindac sulfide, derivs.
 53716-49-7, Carprofen 53716-49-7D, Carprofen, derivs. 60051-81-2
 63170-54-7 80590-83-6 83196-74-1 107254-86-4, NPPB 107254-86-4D,
 5-Nitro-2-(3-phenylpropylamino)benzoic acid, derivs. 176174-97-3
 261766-23-8 261766-24-9 261766-25-0 261766-26-1 261766-27-2
 261766-28-3 261766-29-4 261766-30-7 261766-32-9 261766-35-2
 261766-36-3 261766-37-4 261766-38-5 261766-39-6 261766-40-9
 261766-41-0 261766-42-1 261766-43-2 288854-06-8 288854-11-5

RL: BAC (Biological activity or effector, except adverse);

BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT 158736-49-3, β -Secretase 329900-75-6,
 Cyclooxygenase 2 329967-85-3, Cyclooxygenase 1 338454-52-7,
 γ -Secretase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

IT 9000-81-1, Acetylcholinesterase 338455-07-5, α -Secretase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; NSAID and NSAID derivative amyloid A β 42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) Breitner; US 5643960 A 1997 HCAPLUS
- (2) Clark; US 5695774 A 1997 HCAPLUS
- (3) Garner; US 6160618 A 2000 HCAPLUS
- (4) Horrobin; US 5603959 A 1997 HCAPLUS
- (5) Lee; US 6184248 B1 2001 HCAPLUS
- (6) McGeer; US 5192753 A 1993 HCAPLUS

L43 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:525847 HCAPLUS

DN 135:104271

ED Entered STN: 20 Jul 2001

TI Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses

IN Bienkowski, Michael Jerome; Gurney, Mark E.; Heinrikson, Robert Leroy; Parodi, Luis A.; Yan, Riqiang

PA USA

SO PCT Int. Appl., 185 pp.

CODEN: PIXXD2

DT Patent

LA English

ICI C12

CC 7-2 (Enzymes)

Section cross-reference(s): 3, 9, 14

FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001050829	A2	20010719	WO 2001-IB799	20010509 <--
	WO 2001050829	A3	20031204		
	W: US				
	US 6699671	B1	20040302	US 1999-416901	19991013 <--
	US 2005080232	A1	20050414	US 2003-477076	20010509 <--
PRAI	US 1999-416901	A1	19991013	<--	
	US 1998-101594P	P	19980924	<--	
	US 1999-155493P	P	19990923	<--	
	US 1999-404133	B2	19990923	<--	

WO 1999-US20881 A2 19990923 <--
 WO 2001-IB799 W 20010509

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001050829	ICI	C12
WO 2001050829	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37
US 2005080232	NCL	530/350.000
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37

AB Aspartyl protease 1 (Asp1) and 2 (Asp2) isoforms of β -secretase and their amyloid precursor protein (APP) substrates involved in the formation of amyloid β -peptide ($A\beta$) associated with Alzheimer's disease are provided. A computer method identifying aspartyl proteases in the *Caenorhabditis elegans* genome was used to identify by homol. search human Asp1 and two alternative splice variants of human Asp2. The invention also provides new information about APP processing; cleavage of APP by the β -secretase and γ -secretase generates the N-terminus and C-terminus of the $A\beta$ peptide, resp. Because overprod. of the $A\beta$ peptide has been implicated in the initiation of Alzheimer's disease, inhibitors of the β -secretase have potential in the treatment of Alzheimer's disease. Regions in the proteases critical for their unique function are described, and peptide substrates susceptible to cleavage are characterized. The present invention provides the enzyme and procedures for cleaving sites within the APP protein, as well as associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease. A novel cell line (HEK125.3 cells) for measuring processing of amyloid β peptide form the amyloid protein precursor is also provided by stable transformation of human embryonic kidney 293 cells with a bicistronic vector derived from pIRES-EGFP containing a modified human APP cDNA.

ST secretase amyloid precursor protein processing Alzheimers disease; sequence secretase cDNA human mouse

IT Alzheimer's disease
 Anti-Alzheimer's agents
 Drug screening
 Gene therapy
 Molecular cloning
 Post-translational processing
 (Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Fusion proteins (chimeric proteins)
 RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Amyloid precursor proteins
 RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Antisense oligonucleotides
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line

- (CHO, recombinant host; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT Animal cell line
(HEK125.3, expressing modified APP for processing; Alzheimer's
disease-associated β -secretase and amyloid
precursor protein substrates and their therapeutic uses)
- IT Animal cell line
(Hek 293, recombinant host; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT Animal cell line
(High 5, recombinant host; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT cDNA sequences
(for β -secretase isoforms and modified APP
from mouse and human; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT Proteins, specific or class
RL: ARG (Analytical reagent use); ANST (Analytical
study); USES (Uses)
(green fluorescent, reporter proteins in marker vectors; Alzheimer's
disease-associated β -secretase and amyloid
precursor protein substrates and their therapeutic uses)
- IT Animal cell
(mammalian, recombinant host; Alzheimer's disease-associated
 β -secretase and amyloid precursor protein
substrates and their therapeutic uses)
- IT Protein sequences
(of β -secretase isoforms and modified APP from
mouse and human; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT Escherichia coli
(recombinant host; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT Amyloid
RL: BPR (Biological process); BSU (Biological study,
unclassified); MFM (Metabolic formation); THU
(Therapeutic use); BIOL (Biological study); FORM
(Formation, nonpreparative); PROC (Process); USES (Uses)
(β -; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)
- IT 158736-49-3P, β -Secretase
RL: BAC (Biological activity or effector, except adverse);
BPN (Biosynthetic preparation); BPR (Biological process)
; BSU (Biological study, unclassified); PRP (Properties);
THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); PROC (Process); USES (Uses)
(Asp1 and Asp2(a) and Asp2(b); Alzheimer's disease-associated
 β -secretase and amyloid precursor protein
substrates and their therapeutic uses)
- IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein
moiety reduced) 117910-30-2, Glycoprotein (human clone λ APCP168i4
amyloid A4 precursor protein moiety reduced) 123609-04-1, Glycoprotein
(human clone pGBP2 amyloid A4 precursor protein moiety reduced)
262412-26-0 262412-27-1 262412-28-2 262413-54-7 262413-56-9
262413-61-6, 25: PN: SEQID: 22 unclaimed sequence
262413-63-8 262413-65-0 262413-67-2
262413-69-4 262413-71-8 333371-45-2
333371-47-4 333371-49-6 333371-51-0
RL: ARU (Analytical role, unclassified); BPR (Biological

process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
 (amino acid sequence; Alzheimer's disease-associated β - secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 209209-94-9P, Protein (human gene ASP1) 256364-84-8P, Proteinase Asp2 (Mus musculus precursor) 262412-23-7P 262412-25-9P
 RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (amino acid sequence; Alzheimer's disease-associated β - secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 251080-00-9P 251080-04-3P 262412-22-6P 262412-24-8P
 RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (nucleotide sequence; Alzheimer's disease-associated β - secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 108598-54-5, DNA (human clone 9-110 amyloid A4 glycoprotein cDNA) 262413-58-1 262413-60-5 262413-62-7 262413-66-1 333371-44-1 350264-48-1 350264-49-2 350264-50-5 350264-51-6 350264-52-7 350264-53-8 350264-54-9 350264-55-0 350264-56-1 350264-57-2 350264-58-3 350264-59-4
 RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
 (nucleotide sequence; Alzheimer's disease-associated β - secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 142749-59-5 186142-28-9 252256-37-4 348636-36-2
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (synthetic peptide substrate site; Alzheimer's disease-associated β - secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 118427-80-8 164984-29-6 262364-47-6 262364-48-7 262413-81-0 302566-59-2 333322-60-4 333371-30-5 333371-31-6 333371-32-7 333371-33-8 333371-34-9 333371-35-0 333371-37-2 333371-38-3 333371-39-4 333371-40-7 333371-41-8 333371-42-9 333371-43-0 350241-65-5 350241-67-7 350241-69-9 350241-71-3
 RL: PRP (Properties)
 (unclaimed sequence; Alzheimer's disease-associated β - secretase and amyloid precursor protein substrates and their therapeutic uses)

L43 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2001:507467 HCAPLUS
 DN 135:104269
 ED Entered STN: 13 Jul 2001
 TI Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses
 IN Bienkowski, Michael Jerome; Gurney, Mark E.; Heinrikson, Robert Leroy; Parodi, Luis A.; Yan, Riqiang
 PA USA
 SO PCT Int. Appl., 185 pp.
 CODEN: PIXXD2
 DT Patent
 LA English

ICI C12

CC 7-2 (Enzymes)

Section cross-reference(s): 3, 9, 14

FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001049098	A2	20010712	WO 2001-IB798	20010509 <--
	WO 2001049098	A3	20031120		
	W: US				
	US 6699671	B1	20040302	US 1999-416901	19991013 <--
	US 2004234976	A1	20041125	US 2003-476935	20031106 <--
PRAI	US 1999-416901	A1	19991013	<--	
	US 1998-101594P	P	19980924	<--	
	US 1999-155493P	P	19990923	<--	
	US 1999-404133	B2	19990923	<--	
	WO 1999-US20881	A2	19990923	<--	
	WO 2001-IB798	W	20010509		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2001049098	ICI	C12	
WO 2001049098	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2004234976	NCL	435/006.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--

AB Aspartyl protease 1 (Asp1) and 2 (Asp2) isoforms of β -secretase and their amyloid precursor protein (APP) substrates involved in the formation of amyloid β -peptide ($A\beta$) associated with Alzheimer's disease are provided. A computer method identifying aspartyl proteases in the *Caenorhabditis elegans* genome was used to identify by homol. search human Asp1 and two alternative splice variants of human Asp2. The invention also provides new information about APP processing; cleavage of APP by the β -secretase and γ -secretase generates the N-terminus and C-terminus of the $A\beta$ peptide, resp. Because overprod. of the $A\beta$ peptide has been implicated in the initiation of Alzheimer's disease, inhibitors of the β -secretase have potential in the treatment of Alzheimer's disease. Regions in the proteases critical for their unique function are described, and peptide substrates susceptible to cleavage are characterized. The present invention provides the enzyme and procedures for cleaving sites within the APP protein, as well as associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease. A novel cell line (HEK125.3 cells) for measuring processing of amyloid β peptide from the amyloid protein precursor is also provided by stable transformation of human embryonic kidney 293 cells with a bicistronic vector derived from pIRES-EGFP containing a modified human APP cDNA.

ST secretase amyloid precursor protein processing Alzheimers disease; sequence secretase cDNA human mouse

IT Alzheimer's disease

Anti-Alzheimer's agents

Drug screening

Gene therapy

Molecular cloning

Post-translational processing

(Alzheimer's disease-associated β -secretase and

amyloid precursor protein substrates and their therapeutic uses)

IT Fusion proteins (chimeric proteins)

RL: ARU (Analytical role, unclassified); BPN (Biosynthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

- (Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
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 (Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT Antisense oligonucleotides
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 (CHO, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT Animal cell line
 (HEK125.3, expressing modified APP for processing; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT Animal cell line
 (Hek 293, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT Animal cell line
 (High 5, recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT cDNA sequences
 (for β -secretase isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
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 (of β -secretase isoforms and modified APP from mouse and human; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT Escherichia coli
 (recombinant host; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT Amyloid
 RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process); USES (Uses)
 (β -; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)
- IT 158736-49-3P, β -Secretase
 RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties);

THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (Asp1 and Asp2(a) and Asp2(b); Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein moiety reduced) 117910-30-2, Glycoprotein (human clone λ APCP168i4 amyloid A4 precursor protein moiety reduced) 123609-04-1, Glycoprotein (human clone pGBP2 amyloid A4 precursor protein moiety reduced)
 262412-26-0 262412-27-1 262412-28-2 262413-54-7 262413-56-9
 262413-61-6 262413-63-8 262413-65-0
 262413-67-2 262413-69-4 262413-71-8
 333371-45-2 333371-47-4 333371-49-6 333371-51-0
 RL: ARU (Analytical role, unclassified); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
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 262413-66-1 333371-44-1 350264-48-1 350264-49-2
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 350264-54-9 350264-55-0 350264-56-1 350264-57-2
 350264-58-3 350264-59-4
 RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
 (nucleotide sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 142749-59-5 186142-28-9 252256-37-4 348636-36-2
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (synthetic peptide substrate site; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 118427-80-8 164984-29-6 262364-47-6 262364-48-7 262413-81-0
 302566-59-2 333322-60-4 333371-30-5 333371-31-6 333371-32-7
 333371-33-8 333371-34-9 333371-35-0 333371-37-2 333371-38-3
 333371-39-4 333371-40-7 333371-41-8 333371-42-9 333371-43-0
 350241-65-5 350241-67-7 350241-69-9 350241-71-3
 RL: PRP (Properties)
 (unclaimed sequence; alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

L43 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2001:507466 HCAPLUS
 DN 135:104268
 ED Entered STN: 13 Jul 2001
 TI Alzheimer's disease-associated β -secretase and
 amyloid precursor protein substrates and their therapeutic uses
 IN Bienkowski, Michael Jerome; Gurney, Mark E.; Heinrikson, Robert Leroy;
 Parodi, Luis A.; Yan, Riqiang
 PA USA
 SO PCT Int. Appl., 185 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 ICI C12
 CC 7-2 (Enzymes)

Section cross-reference(s): 3, 9, 14

FAN.CNT 8

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001049097	A2	20010712	WO 2001-IB797	20010509 <--
	WO 2001049097	A3	20031120		
	W: US				
	US 6699671	B1	20040302	US 1999-416901	19991013 <--
	US 2003077226	A1	20030424	US 2001-869414	20010627
	US 6790610	B2	20040914		
PRAI	US 1999-416901	A1	19991013	<--	
	US 1998-101594P	P	19980924	<--	
	US 1999-155493P	P	19990923	<--	
	US 1999-404133	B2	19990923	<--	
	WO 1999-US20881	A2	19990923	<--	
	WO 2001-IB797	W	20010509		

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PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 2001049097	ICI	C12	
WO 2001049097	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 6699671	NCL	435/007.100; 530/300.000; 530/350.000	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	<--
US 2003077226	NCL	424/009.600	
	ECLA	C07K014/47A3; C12N009/64F2C23; C12Q001/37	

AB Aspartyl protease 1 (Asp1) and 2 (Asp2) isoforms of β -secretase and their amyloid precursor protein (APP) substrates involved in the formation of amyloid β -peptide ($A\beta$) associated with Alzheimer's disease are provided. A computer method identifying aspartyl proteases in the *Caenorhabditis elegans* genome was used to identify by homol. search human Asp1 and two alternative splice variants of human Asp2. The invention also provides new information about APP processing; cleavage of APP by the β -secretase and γ -secretase generates the N-terminus and C-terminus of the $A\beta$ peptide, resp. Because overprodn. of the $A\beta$ peptide has been implicated in the initiation of Alzheimer's disease, inhibitors of the β -secretase have potential in the treatment of Alzheimer's disease. Regions in the proteases critical for their unique function are described, and peptide substrates susceptible to cleavage are characterized. The present invention provides the enzyme and procedures for cleaving sites within the APP protein, as well as associated nucleic acids, peptides, vectors, cells and cell isolates and assays. The invention further provides a modified APP protein and associated nucleic acids, peptides, vectors, cells, and cell isolates, and assays that are particularly useful for identifying candidate therapeutics for treatment or prevention of Alzheimer's disease. A novel cell line (HEK125.3 cells) for measuring processing of amyloid β peptide form the amyloid protein precursor is also provided by stable transformation of human embryonic kidney 293 cells with a bicistronic vector derived from pIRES-EGFP containing a modified human APP cDNA.

ST secretase amyloid precursor protein processing Alzheimers disease;
sequence secretase cDNA human mouse

IT **Alzheimer's disease**
Anti-Alzheimer's agents
Drug screening
Gene therapy
Molecular cloning
Post-translational processing
(Alzheimer's disease-associated β -secretase and
amyloid precursor protein substrates and their therapeutic uses)

IT Fusion proteins (chimeric proteins)
RL: ARU (Analytical role, unclassified); BPN (Biosynthetic
preparation); THU (Therapeutic use); ANST (Analytical
study); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(Alzheimer's disease-associated β -secretase and
amyloid precursor protein substrates and their therapeutic uses)

IT **Amyloid precursor proteins**
RL: BPN (Biosynthetic preparation); BPR (Biological
process); BSU (Biological study, unclassified); THU
(Therapeutic use); BIOL (Biological study); PREP
(Preparation); PROC (Process); USES (Uses)
(Alzheimer's disease-associated β -secretase and
amyloid precursor protein substrates and their therapeutic uses)

IT Antisense oligonucleotides
RL: THU (Therapeutic use); BIOL (Biological study);
USES (Uses)
(Alzheimer's disease-associated β -secretase and
amyloid precursor protein substrates and their therapeutic uses)

IT Animal cell line
(CHO, recombinant host; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT Animal cell line
(HEK125.3, expressing modified APP for processing; Alzheimer's
disease-associated β -secretase and amyloid
precursor protein substrates and their therapeutic uses)

IT Animal cell line
(Hek 293, recombinant host; Alzheimer's disease-associated β
-secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT Animal cell line
(High 5, recombinant host; Alzheimer's disease-associated β
-secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT cDNA sequences
(for β -secretase isoforms and modified APP
from mouse and human; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT Proteins, specific or class
RL: ARG (Analytical reagent use); ANST (Analytical
study); USES (Uses)
(green fluorescent, reporter proteins in marker vectors; Alzheimer's
disease-associated β -secretase and amyloid
precursor protein substrates and their therapeutic uses)

IT Animal cell
(mammalian, recombinant host; Alzheimer's disease-associated
 β -secretase and amyloid precursor protein
substrates and their therapeutic uses)

IT Protein sequences
(of β -secretase isoforms and modified APP from
mouse and human; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT Escherichia coli

(recombinant host; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT Amyloid

RL: BPR (Biological process); BSU (Biological study,
unclassified); MFM (Metabolic formation); THU
(Therapeutic use); BIOL (Biological study); FORM
(Formation, nonpreparative); PROC (Process); USES (Uses)
(β -; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT 158736-49-3P, β -Secretase

RL: BAC (Biological activity or effector, except adverse);
BPN (Biosynthetic preparation); BPR (Biological process)
; BSU (Biological study, unclassified); PRP (Properties);
THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); PROC (Process); USES (Uses)
(Asp1 and Asp2(a) and Asp2(b); Alzheimer's disease-associated
 β -secretase and amyloid precursor protein
substrates and their therapeutic uses)

IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein
moiety reduced) 117910-30-2, Glycoprotein (human clone λ APCP168i4
amyloid A4 precursor protein moiety reduced) 123609-04-1, Glycoprotein
(human clone pGBP2 amyloid A4 precursor protein moiety reduced)
262412-26-0 262412-27-1 262412-28-2 262413-54-7 262413-56-9
262413-61-6, 25: PN: SEQID: 22 unclaimed sequence
262413-63-8 262413-65-0 262413-67-2
262413-69-4 262413-71-8 333371-45-2
333371-47-4 333371-49-6 333371-51-0
RL: ARU (Analytical role, unclassified); BPR (Biological
process); BSU (Biological study, unclassified); BUU
(Biological use, unclassified); PRP (Properties); ANST
(Analytical study); BIOL (Biological study); PROC (Process)
; USES (Uses)

(amino acid sequence; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT 209209-94-9P, Protein (human gene ASP1) 256364-84-8P,
Proteinase Asp2 (Mus musculus precursor) 262412-23-7P
262412-25-9P

RL: BAC (Biological activity or effector, except adverse);
BPN (Biosynthetic preparation); BPR (Biological process)
; BSU (Biological study, unclassified); PRP (Properties);
THU (Therapeutic use); BIOL (Biological study); PREP
(Preparation); PROC (Process); USES (Uses)
(amino acid sequence; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT 251080-00-9P 251080-04-3P 262412-22-6P
262412-24-8P

RL: BPN (Biosynthetic preparation); PRP (Properties); THU
(Therapeutic use); BIOL (Biological study); PREP
(Preparation); USES (Uses)
(nucleotide sequence; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

IT 108598-54-5, DNA (human clone 9-110 amyloid A4 glycoprotein cDNA)
262413-58-1 262413-60-5 262413-62-7
262413-66-1 333371-44-1 350264-48-1 350264-49-2
350264-50-5 350264-51-6 350264-52-7 350264-53-8
350264-54-9 350264-55-0 350264-56-1 350264-57-2
350264-58-3 350264-59-4
RL: BUU (Biological use, unclassified); PRP (Properties);
BIOL (Biological study); USES (Uses)
(nucleotide sequence; Alzheimer's disease-associated β -
secretase and amyloid precursor protein substrates and their
therapeutic uses)

therapeutic uses)

IT 142749-59-5 186142-28-9 252256-37-4 348636-36-2
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (synthetic peptide substrate site; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 262413-81-0 333371-30-5 333371-31-6 333371-32-7 333371-33-8
 333371-34-9 333371-35-0 333371-37-2 333371-38-3
 RL: PRP (Properties) (unclaimed nucleotide sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

IT 118427-80-8 164984-29-6 262364-47-6 262364-48-7 302566-59-2
 333322-60-4 333371-39-4 333371-40-7 333371-41-8 333371-42-9
 333371-43-0 350241-65-5 350241-67-7 350241-69-9 350241-71-3
 RL: PRP (Properties) (unclaimed sequence; Alzheimer's disease-associated β -secretase and amyloid precursor protein substrates and their therapeutic uses)

L43 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 2000:513905 HCAPLUS
 DN 133:133772
 ED Entered STN: 28 Jul 2000
 TI Rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening
 IN Bamdad, Cynthia Carol; Bamdad, R. Shoshana
 PA Minerva Biotechnologies Corporation, USA
 SO PCT Int. Appl., 76 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM G01N033-68
 CC 14-10 (Mammalian Pathological Biochemistry)
 Section cross-reference(s): 1, 15, 17
 FAN.CNT 5

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000043791	A2	20000727	WO 2000-US1997	20000125 <--
	WO 2000043791	A3	20010726		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	CA 2361013	AA	20000727	CA 2000-2361013	20000125 <--
	EP 1169646	A2	20020109	EP 2000-913266	20000125 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
	JP 2002540383	T2	20021126	JP 2000-595161	20000125 <--
	US 2005112607	A1	20050526	US 2004-823097	20040413 <--
PRAI	US 1999-117126P	P	19990125	<--	
	US 1999-132288P	P	19990503	<--	
	US 1999-155937P	P	19990924	<--	
	US 1999-116975P	P	19990123	<--	
	US 1999-132289P	P	19990503	<--	
	US 1999-133148P	P	19990507	<--	
	US 1999-133772P	P	19990512	<--	
	WO 2000-US1504	A2	20000121	<--	
	WO 2000-US1997	W	20000125	<--	
	US 2000-602689	B2	20000623	<--	

US 2000-602778 B2 20000623 <--
 US 2000-631818 B2 20000803 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000043791	ICM	G01N033-68
WO 2000043791	ECLA	G01N033/68V2
US 2005112607	NCL	435/006.000
	ECLA	C12Q001/00B; C12Q001/00B4; G01N033/543D; G01N033/543K2B; G01N033/543M; G01N033/58H; G01N033/68V2

AB Methods, assays, and components are described in which biol. samples can be rapidly and sensitively analyzed for the presence of species associated with neurodegenerative disease. Techniques and components are provided for diagnosis of disease, as well as for screening of candidate drugs for treatment of neurodegenerative disease. The techniques are simple, extremely sensitive, and utilize readily-available components. Binding species, capable of binding a neurodegenerative disease aggregate-forming or fibril-forming species, are fastened to surfaces of electrodes and surfaces of particles, or provided free in solution, to bind fibril-forming species and/or be involved in aggregation.

ST aberrant protein fibril aggregation colloid; drug screening neurodegenerative disease kit

IT Brain, disease
 Prion diseases
 (Creutzfeldt-Jakob; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
 (PrPSc; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
 RL: ANT (Analyte); ANST (Analytical study)
 (PrPSc; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Voltammetry
 (a.c.; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Prion proteins
 RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
 (bovine spongiform encephalopathy; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Nervous system
 (degeneration; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Self-assembled monolayers
 (electroactive; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Carboxyl group
 (ionized; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

IT Aggregation
 Alzheimer's disease
 Blood analysis
 Cerebrospinal fluid
 Colloids
 Diagnosis
 Drug screening
 Feed
 Fibril
 Immobilization, biochemical
 Magnetic particles

Microtiter plates
 Molecular association
 Molecular recognition
 Parkinson's disease
 Test kits
 Transplant and Transplantation
 (rapid and sensitive detection of aberrant protein(fibril) aggregation
 in neurodegenerative disease diagnosis and drug screening)

IT Enzymes, biological studies
 RL: BSU (Biological study, unclassified); PEP (Physical,
 engineering or chemical process); PRP (Properties); BIOL (Biological
 study); PROC (Process)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation
 in neurodegenerative disease diagnosis and drug screening)

IT Antibodies
 DNA
 Metalloenes
 Nucleic acids
 Oligonucleotides
 Peptides, properties
 Proteins, general, properties
 RL: PEP (Physical, engineering or chemical process); PRP (Properties);
 PROC (Process)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation
 in neurodegenerative disease diagnosis and drug screening)

IT Brain, disease
 (spongiform encephalopathy, transmissible; rapid and sensitive
 detection of aberrant protein(fibril) aggregation in neurodegenerative
 disease diagnosis and drug screening)

IT Sensors
 (surface plasmon resonance chip; rapid and sensitive detection of
 aberrant protein(fibril) aggregation in neurodegenerative disease
 diagnosis and drug screening)

IT Transferrins
 RL: BSU (Biological study, unclassified); PEP (Physical,
 engineering or chemical process); PRP (Properties); BIOL (Biological
 study); PROC (Process)
 (τ -transferrins; rapid and sensitive detection of aberrant
 protein(fibril) aggregation in neurodegenerative disease diagnosis and
 drug screening)

IT Amyloid
 RL: BPR (Biological process); BSU (Biological study,
 unclassified); BIOL (Biological study); PROC (Process)
 (β -, C-terminal fragment; rapid and sensitive detection of
 aberrant protein(fibril) aggregation in neurodegenerative disease
 diagnosis and drug screening)

IT Amyloid
 RL: BSU (Biological study, unclassified); PEP (Physical,
 engineering or chemical process); PRP (Properties); BIOL (Biological
 study); PROC (Process)
 (β -; rapid and sensitive detection of aberrant protein(fibril)
 aggregation in neurodegenerative disease diagnosis and drug screening)

IT 58-85-5, Biotin 70-18-8, Glutathione, properties 102-54-5, Ferrocene
 573-58-0, Congo Red 2390-54-7, Thioflavin-T 6066-82-6, Succinimide,
 N-hydroxy 7440-57-5, Gold, properties 9001-78-9, Phosphatase, alkaline
 9013-20-1, Streptavidin 158736-49-3, Secretase
 RL: PEP (Physical, engineering or chemical process); PRP (Properties);
 PROC (Process)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation
 in neurodegenerative disease diagnosis and drug screening)

IT 139-13-9, Nitrilotriacetic acid 10487-90-8 64691-70-9
 RL: PEP (Physical, engineering or chemical process); PRP (Properties); RCT
 (Reactant); PROC (Process); RACT (Reactant or reagent)
 (rapid and sensitive detection of aberrant protein(fibril) aggregation
 in neurodegenerative disease diagnosis and drug screening)

IT 167396-02-3 286411-43-6 286411-44-7 286411-46-9 286411-47-0

286411-48-1

RL: PRP (Properties)

(unclaimed sequence; rapid and sensitive detection of aberrant protein(fibril) aggregation in neurodegenerative disease diagnosis and drug screening)

L43 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:493661 HCAPLUS

DN 133:117175

ED Entered STN: 21 Jul 2000

TI Methods and compositions for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β - APP)

IN Seiffert, Dietmar A.; Mitchell, Thomas J.

PA Dupont Pharmaceuticals Company, USA

SO PCT Int. Appl., 42 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N

CC 9-10 (Biochemical Methods)

Section cross-reference(s): 1, 3, 6

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000042166	A2	20000720	WO 2000-US872	20000113 <--
	W: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, VN, ZA				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6518011	B1	20030211	US 2000-481980	20000112 <--
	AU 2000034711	A1	20000801	AU 2000-34711	20000113 <--
	US 2003091983	A1	20030515	US 2002-326049	20021220 <--
PRAI	US 1999-115749P	P	19990113	<--	
	US 2000-481980	A3	20000112	<--	
	WO 2000-US872	W	20000113	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000042166	ICM	C12N
WO 2000042166	ECLA	C07K014/47A3; G01N033/68V2 <--
US 6518011	NCL	435/004.000; 435/007.100; 435/007.210; 435/069.100; 435/070.100; 435/320.100; 435/325.000; 530/300.000; 530/350.000
	ECLA	C07K014/47A3; G01N033/68V2 <--
US 2003091983	NCL	435/004.000
	ECLA	C07K014/47A3; G01N033/68V2 <--

AB The present invention is directed generally to methods and composition for monitoring the processing of epitope-tagged β -APP. More specifically, the present invention relates to the use of such methods and composition for monitoring responses of cells expressing such epitope-tagged β -APP or fragments thereof or cell free systems containing the epitope-tagged polypeptides to therapy of diseases associated with an altered metabolism of the β -APP, and for screening and evaluation of potential drugs for the treatment of these disorders, including Alzheimer's disease (AD). Site-directed mutagenesis was used to incorporate the cDNA sequence for either the myc or HA 11 epitope tag within the A- β fragment of the β -APP 695 isoform. After HEK 293 cells were transfected with the construct, the cell lysates were analyzed by immunoblotting.

ST cellular processing epitope tagged beta amyloid precursor protein; drug screening epitope tagged beta amyloid precursor protein

IT Animal cell line
(293; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β - APP))

- IT Amyloid precursor proteins
 RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (APP695, with myc or HA 11 epitope tag in A- β part; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Antibodies
 RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
 (as binding substances binding to epitope tag or other epitope; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Biopolymers
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (as test compds. methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Gene, animal
 RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (c-myc, as epitope tag; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT cDNA
 RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
 (encoding epitope-tagged β -amyloid precursor protein; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Immunoassay
 (enzyme-linked immunosorbent assay; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Hemagglutinins
 RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (epitope HA 11 of, of influenza, as epitope tag; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Protein degradation
 (epitope tag as target for; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Fluids
 (epitope-tagged A- β peptides detection in; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Peptides, analysis
 RL: ANT (Analyte); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PUR (Purification or recovery); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC

- (Process)
(epitope-tagged A- β , detection of; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Amyloid precursor proteins
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(epitope-tagged; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Animal cell line
(expressing cDNA construct; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Animal tissue
(exts.; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Mutation
(forms of β -APP, epitope tag in relation to; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Immunoassay
(immunoblotting; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Ascitic fluid
Blood
Blood analysis
Cell
Cerebrospinal fluid
Culture media
Drug screening
Epitopes
Molecular cloning
Protein sequences
Urine
Urine analysis
(methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Antibodies
RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(monoclonal, as binding substances binding to epitope tag or other epitope; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Anti-Alzheimer's agents
(screening for and evaluation of; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Molecules
(small, as test compds.; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT Mutation
(splice site, forms of β -APP, epitope tag in relation to; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))
- IT 284025-86-1P

RL: ARU (Analytical role, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); PREP (Preparation)

(as synthetic HA 11 A- β peptide; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

IT 88191-84-8, MDL 28170

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(as γ -secretase inhibitor, transformed HEK 293 cells response to; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

IT 158736-49-3, β -Secretase

RL: ARU (Analytical role, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(binding substance to neoepitope generated by; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

IT 20350-15-6, Brefeldin A

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(transformed HEK 293 cells response to; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

IT 284507-22-8, 3: PN: WO0042166 PAGE: 22 unclaimed DNA 284507-23-9, 4: PN: WO0042166 PAGE: 22 unclaimed DNA

RL: PRP (Properties)

(unclaimed nucleotide sequence; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

IT 134500-80-4 284507-21-7

RL: PRP (Properties)

(unclaimed protein sequence; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

IT 92000-76-5 205437-69-0 284494-16-2

RL: PRP (Properties)

(unclaimed sequence; methods and compns. for monitoring cellular processing of epitope-tagged β -amyloid precursor protein (β -APP))

L43 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:53695 HCAPLUS

DN 132:102848

ED Entered STN: 23 Jan 2000

TI Interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease

IN Nandabalan, Krishnan; Yang, Meijia; Schulz, Vincent Peter

PA Curagen Corporation, USA

SO PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07K014-00

CC 1-11 (Pharmacology)

Section cross-reference(s): 3, 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000002911	A2	20000120	WO 1999-US15592	19990708 <--
	WO 2000002911	A3	20010118		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,			

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
 MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,
 TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,
 MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
 ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
 CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 CA 2332625 AA 20000120 CA 1999-2332625 19990708 <--
 AU 9948693 A1 20000201 AU 1999-48693 19990708 <--
 EP 1095154 A2 20010502 EP 1999-932376 19990708 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO
 JP 2002521004 T2 20020716 JP 2000-559140 19990708 <--
 PRAI US 1998-113348 A2 19980710 <--
 WO 1999-US15592 W 19990708 <--

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000002911	ICM	C07K014-00
WO 2000002911	ECLA	C07K014/47A3; C07K014/81B1A; C12N009/64F2C21 <--
AB	The present invention discloses an interaction between β - APP and HsLON and the formation of a β -APP :HsLON complex, or of the derivs., fragments, analogs and homologs thereof, that were identified using a modified, improved yeast two hybrid assay system. Methodologies of screening these aforementioned complexes for efficacy in treating and/or preventing various diseases and disorders, particularly neurodegenerative disease, cardiomyopathy, diabetes, hearing loss, male infertility, mitochondrial DNA mutation associated disorders and the like, are also disclosed herein.	
ST	Alzheimer beta amyloid precursor Lon protease HsLON sequence	
IT	Proteins, specific or class RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses) (HsLON (human Lon-protease-like protein); interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Gene, animal RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation) (HsLON; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Diagnosis (agents; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Heart, disease (cardiomyopathy; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Drug delivery systems (carriers; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Nervous system (degeneration; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Mutation (in mitochondrial DNA; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)	
IT	Alzheimer's disease	

Antidiabetic agents
 Diabetes mellitus
 Diagnosis
 Drug screening
 Fluorescent indicators
 Genetic vectors
 Molecular cloning
 Protein sequences
 cDNA sequences
 (interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Fusion proteins (chimeric proteins)
 RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Amyloid precursor proteins
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
 (interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Primers (nucleic acid)
 Probes (nucleic acid)
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Antisense oligonucleotides
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Hearing
 (loss; interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Fertility
 (male, disorder; interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Mitochondrial DNA
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
 (mutation in; interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Promoter (genetic element)
 RL: PEP (Physical, engineering or chemical process); PROC (Process)
 (of gene HsLON; interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Mutagenesis
 (site-directed; interaction of human beta amyloid precursor protein (β - APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT RNA
 RL: BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (β -APP- or HsLON-encoding; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Antibodies
 RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
 (β -APP-HsLON complex-specific; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT Gene, animal
 RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
 (β -APP; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT 108598-76-1, Glycoprotein (human clone 9-110 amyloid A4 precursor protein moiety reduced) 155078-43-6
 RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
 (amino acid sequence; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT 151002-40-3, GenBank A02759 151579-59-8, GenBank X74215
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
 (nucleotide sequence; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

IT 255815-97-5, 1: PN: WO0002911 SEQID: 5 unclaimed DNA 255815-98-6, 2: PN: WO0002911 SEQID: 6 unclaimed DNA
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; interaction of human beta amyloid precursor protein (β -APP) with human Lon-protease-like protein (HsLON) in relation to treating Alzheimer's disease)

L43 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2005 ACS on STN
 AN 1999:795957 HCAPLUS
 DN 132:32677
 ED Entered STN: 17 Dec 1999
 TI β -secretases acting on wild-type forms of amyloid precursor protein
 IN Rholam, Mohamed; Munoz-Gimenez, Noeli; Moutaouakil, Mohamed; Cohen, Paul; Bertrand, Philippe
 PA Rhone-Poulenc Rorer S.A., Fr.; Universite Pierre et Marie Curie Paris VI
 SO PCT Int. Appl., 45 pp.
 CODEN: PIXXD2
 DT Patent
 LA French
 IC ICM C12N015-12
 ICS C12N015-57; C12N009-64; C07K016-40; C12Q001-37; A61K039-395; A61K038-48; A61K031-70
 CC 7-2 (Enzymes)
 Section cross-reference(s): 1, 14

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9964587	A1	19991216	WO 1999-FR1326	19990604 <--
	W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	FR 2779444	A1	19991210	FR 1998-7068	19980605 <--
	CA 2330242	AA	19991216	CA 1999-2330242	19990604 <--
	AU 9940455	A1	19991230	AU 1999-40455	19990604 <--
	EP 1084240	A1	20010321	EP 1999-923674	19990604 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
	JP 2002517239	T2	20020618	JP 2000-553577	19990604 <--
	ZA 2000007118	A	20020201	ZA 2000-7118	20001201 <--
PRAI	FR 1998-7068	A	19980605	<--	
	US 1999-122599P	P	19990331	<--	
	WO 1999-FR1326	W	19990604	<--	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9964587	ICM	C12N015-12
	ICS	C12N015-57; C12N009-64; C07K016-40; C12Q001-37; A61K039-395; A61K038-48; A61K031-70
WO 9964587	ECLA	C12N009/64F <--
FR 2779444	ECLA	C12N009/64F <--

AB β -Secretases that cleave the natural

β -amyloid peptide precursor (APP) are identified and characterized. The enzyme may be of use in the treatment of Alzheimer's disease (no data) or in screening for effectors of precursor processing. The enzyme cleaves the protein between methionine-596 and aspartic acid-597 of the wild-type amyloid precursor but not the asparagine-595-leucine-596 double mutant. The enzyme is found in cells not affected by Alzheimer's disease, it has a mol. weight of 70,000 and a pI of .apprx.6.0. The enzyme is a chymotrypsin-like serine proteinase. The enzyme was identified in THP-1 cells that were identified as producing properly cleaved amyloid precursor. Purification was monitored by cleavage of an assay substrate and checking for the correct cleavage product with a monoclonal antibody. Anal. of substrate specificity using a number of analogs of the cleavage site confirmed the activity and specificity of the enzyme.

ST secretase beta wild type amyloid precursor protein cleavage; Alzheimer disease beta secretase regulation amyloid processing

IT Animal cell line

(THP-1, β -secretase of; β -secretases acting on wild-type forms of amyloid precursor protein)

IT Alzheimer's disease

(amyloid precursor processing and treatment of; β -secretases acting on wild-type forms of amyloid precursor protein)

IT Nervous system

(central, manufacture of β -secretase in cells of; β -secretases acting on wild-type forms of amyloid precursor protein)

IT Nervous system

(degeneration, amyloid precursor processing and treatment of; β -secretases acting on wild-type forms of amyloid precursor protein)

IT Drug screening

(for inhibitors of β -secretase; β -secretases acting on wild-type forms of amyloid precursor protein)

IT Nicotinic receptors
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (in secretion and delivery of β -secretase;
 β -secretases acting on wild-type forms of amyloid precursor protein)

IT Signal peptides
 RL: BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (in secretion and delivery of β -secretase;
 β -secretases acting on wild-type forms of amyloid precursor protein)

IT Immune system
 (manufacture of β -secretase in cells of;
 β -secretases acting on wild-type forms of amyloid precursor protein)

IT Nervous system
 (peripheral, manufacture of β -secretase in cells of;
 β -secretases acting on wild-type forms of amyloid precursor protein)

IT Immunoglobulins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (signal peptides of κ -chain of, in secretion and delivery of β -secretase;
 β -secretases acting on wild-type forms of amyloid precursor protein)

IT Antibodies
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (to β -secretase; β -secretases acting on wild-type forms of amyloid precursor protein)

IT Amyloid precursor proteins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (β -secretases acting on wild-type forms of amyloid precursor protein)

IT 118427-80-8 186142-28-9 252256-37-4 252256-38-5
 252256-39-6 252256-40-9 252256-41-0 252256-42-1 252256-43-2
 252256-44-3 252256-45-4 252256-46-5 252256-47-6 252256-48-7
 252256-49-8 252333-20-3 252333-21-4
 RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
 (cleavage by β -secretase of; β -secretases acting on wild-type forms of amyloid precursor protein)

IT 158736-49-3P, β -Secretase
 RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process)
 (β -secretases acting on wild-type forms of amyloid precursor protein)

RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
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- (2) Athena Neurosciences Inc; WO 9640885 A 1996 HCAPLUS
- (3) Brown, A; JOURNAL OF NEUROCHEMISTRY 1996, V66(6), P2436 HCAPLUS
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- (8) Nelson, R; JOURNAL OF BIOLOGICAL CHEMISTRY 1990, V265(7), P3836 HCAPLUS
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